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THE MONOCYTE IN ACTIVE TUBERCULOSIS

SUPRAVITAL STUDIES OF THE BLOOD *

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In using the term monocyte to designate the white blood cell commonly known as the transitional or large mononuclear cell, we are following the nomenclature and classification of Sabin, Cunningham and Doan.[1] These investigators stated that two types of mononuclear cells, namely, the monocyte and the clasmatocyte, can be differentiated by means of the "supravital" staining technic. They believed that these cells have a different anatomic origin, but, under certain circumstances, the common function of phagocytosis. The monocyte arises from a primitive stem cell, which in turn comes from the reticular cells in the bone marrow, spleen and lymph glands. This primitive cell is also the parent stem from which the leukocytic and lymphatic series of cells are derived. The clasmatocyte arises from the cells which come from the endothelium, lining the sinuses of the lymph nodes, the sinusoids of the liver lobules and the capillaries of bone marrow, suprarenal cortex and hypophysis. The erythrocytic series of cells also are derived from endothelium.

The monocyte seen in living preparation stained with neutral red and Janus green is a fairly large (10 to 15 microns), usually round cell, with an oval or slightly indented nucleus, usually eccentrically placed. In the mature cell, there is a small ring of granules situated near the identation or "hof" of the nucleus. This ring of granules surrounding the centrosphere of the cell, a small, clear, nonstaining area, is made up of two or three concentric circles, forming a "roset." These granules

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1. Sabin, F. R.; Cunningham, R. S., and Doan, C. A.: The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem Cell in Adult Tissues, publ. 361, Contributions to Embriology, 84, p. 227, Carnegie Inst., Washington.

take the neutral red stain. Further out, on the periphery of the cell, there may be a variable number of small greenish-staining particles, which are mitachondria, and occasionally large, round, red bodies, the vacuoles, which are evidence of phagocytic activity. These vacuoles are necessarily at the periphery of the cell, for the roset cannot be displaced from the center. The specifically differentiating points between the monocyte and clasmatocyte are the arrangement of granules in the roset and the arrangement of the vacuoles. To emphasize this point, the monocyte has a definite centrosphere about which the red granules are arranged in a roset and the vacuoles are arranged peripheral to the roset, whereas, the clasmatocyte does not have a roset and the first vacuoles are immediately adjacent to the nucleus. In the fixed smear, as pointed out by Sabin, the roset in the monocyte is dissolved by alcohol fixation, so that the typical pattern of granules is not visible and the cell is not readily distinguished from the clasmatocyte. The latter cell has been designated by Mallory as the endothelial leukocyte, by Aschoff and Kiyono as the histiocyte and by Lewis as the macrophage.

In 1925, Cunningham, Sabin, Sugiyama and Kindwall [2] called attention to the rôle of the monocyte in tuberculosis. They studied the effect of tuberculosis in the tissues and in the blood stream of rabbits. Their investigations showed that the injection of living tubercle bacilli into the blood stream (or intraperitoneally) causes an overproduction of the reticular cells in the tissues and that the monocytes which arise from these cells increase and undergo modifications with the development of the epithelioid and giant cells, so characteristic of the lesion in tuberculosis. This reaction is a local one in the tissues. It is reflected in the blood stream by an increase of monocytes and by the appearance of modified forms of monocytes and epithelioid cells. In undergoing this modification, the monocyte becomes less active and nonmotile, and the roset of granules around the centrosphere becomes larger and more compact. The typical epithelioid cell is, therefore, a much larger monocyte with a large roset. These changes are described and illustrated by the authors.[2] It must be kept in mind that the recognition of these cells in the blood stream was made possible by the supravital technic. The authors also found that in rabbits there is a constant correlation between the activity of the process and the total number of monocytes and modified monocytes in the blood stream. In actively progressive tuberculosis, the monocytes increase, in some instances forming 50 per cent of the total number of white cells, and the normal ratio between monocyte and lymphocyte is reversed. In arrested or healing tuberculosis, the total

2. Cunningham, R. S.; Sabin, F. R.; Sugiyama, S., and Kindwall, J. A.: Rôle of the Monocyte in Tuberculosis, Bull. Johns Hopkins Hosp. **37**:231 (Oct.) 1925.

number of monocytes falls, and the ratio between monocytes and lymphocytes returns to normal. Still another group of animals showed a repeatedly shifting ratio between monocytes and lymphocytes, according to the activity or healing of the tuberculous process.

It was apparent from these experimental studies that significant changes in the blood might be expected in human cases, according to the activity of the lesion. This has been found to be true. In recent communications, Cunningham and Tompkins [3] and Rogers [4] found that the monocyte-lymphocyte ratio and the presence of modified monocytes and epithelioid cells were of more than academic interest, and that such changes in the blood were a useful aid in the diagnosis and prognosis of tuberculosis in man. That conflicting views are held regarding the importance of such changes in the blood is not surprising when one takes into consideration the various stages of tuberculosis that have been investigated.

The observations of Cunningham and others stimulated us to study, by the supravital staining method, the peripheral blood of patients with tuberculosis. We chose patients with acute miliary tuberculosis for our preliminary study, as this form of tuberculosis in infants and children is similar to, if not identical with, the tuberculosis experimentally produced by Cunningham, Sabin and others, in rabbits.

The purpose of this communication is to report the results of the changes in the blood of seventeen patients. The patients may be divided into two groups: patients with proved tuberculosis (group 1) and patients with probable tuberculosis diagnosed clinically but not proved (group 2).

In group 1, there were twelve patients. The diagnosis of active tuberculosis in this group was confirmed at necropsy in six patients, by inoculation into guinea-pigs in one patient, by biopsy in three patients and by roentgenograms and finding the organism in two patients. The type of tuberculosis from which these patients were suffering is shown in table 1.

In group 2 there were five patients. The diagnosis was not confirmed positively by the reaction to tuberculin, roentgenograms, the presence of tubercle bacilli, biopsy or other means. The data concerning this group are indicated in table 2.

In these studies, we have followed the supravital technic described by Sabin, and we have used as the normal percentage of monocytes and lymphocytes, and the ratio of these two to each other, for the different

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3. Cunningham, R. S., and Tompkins, E. H.: White Blood Cells in Human Tuberculosis, Am. Rev. Tuberc. **17**:204 (March) 1928.

4. Rogers, Philip M.: A Study of the Blood Monocyte in Children with Tuberculosis, New England J. M. **198**:740, 1928.

TABLE 1.—*Group 1—Proved Cases of Tuberculosis*

Case	Name	Age	Type of Tuberculosis	Diagnosis Confirmed by	Result	Date	White Blood Cells	Monocytes		Lymphocytes		Comparison Monocyte-Lymphocyte	
								Per Cent	Total	Per Cent	Total	Ratio	Per Cent
1	B. M.	14 mos.	Acute miliary	Roentgenogram; tuberculin test	Died	12/ 2	17,000	10	1,700	15	2,550	1:1.50	0.67
						12/ 8	15,000	25	3,750	12	1,800	1:0.48	2.08
2	G. C.	3 mos.	Acute miliary	Necropsy	Died	1/21	9,000	14	1,260	26	2,340	1:1.86	0.53
						1/27	10,000	13	1,300	15	1,500	1:1.15	0.83
						1/29	12,000	13	1,560	9	1,080	1:0.69	1.43
3	R. S.	4 mos.	Acute miliary, with meningitis	Necropsy	Died	3/ 5	18,000	7	1,260	21	3,780	1:3.0	0.33
						3/10	20,000	22	4,400	17	3,400	1:0.77	1.30
						3/15	20,000	14	2,800	6	1,200	1:0.50	2.33
4	C. E.	17 mos.	Acute miliary, with meningitis	Necropsy	Died	1/17	18,000	13	2,340	11	1,980	1:0.85	1.18
						1/22	20,000	19	3,800	15	3,000	1:0.79	1.27
						1/24	20,000	22	4,400	9	1,800	1:0.41	2.44
5	I. N.	18 mos.	Acute miliary, with meningitis	Necropsy	Died	4/12	13,000	12	1,560	20	2,600	1:1.67	0.60
						4/16	20,000	13	2,600	14	2,800	1:1.07	0.93
						4/18	26,000	14	3,640	12	3,120	1:0.86	1.17
6	C. A.	8 mos.	Acute miliary, with meningitis	Necropsy	Died	3/ 5	11,000	11	1,210	12	1,320	1:1.09	0.91
						3/ 9	20,000	17	3,400	10	2,000	1:0.59	1.70
7	C. T.	13 mos.	Acute miliary, with meningitis	Roentgenogram; tuberculin test negative; tubercle bacilli	Died	12/ 7	12,000	14	1,680	13	1,560	1:0.93	1.01
8	E. P.	9 yrs.	Generalized	Roentgenogram; tubercle bacilli; necropsy	Died	3/31	15,000	12	1,800	15	2,250	1:1.25	0.80
						4/ 5	12,000	11	1,320	40	4,800	1:3.64	0.28
						4/12	11,000	18	1,980	12	1,320	1:0.67	1.50
9	E. F.	9 yrs.	Peritonitis	Laparotomy; biopsy	Living	11/ 4	9,000	12	1,080	8	720	1:0.67	1.50
						11/14	12,000	16	1,920	9	1,080	1:0.56	1.78
						11/25	10,000	5	500	30	3,000	1:6.0	0.17
						12/ 2	10,000	2	200	33	3,800	1:19.0	0.05
10	S. S.	8 yrs.	Peritonitis	Laparotomy; biopsy	Living	3/22	15,000	13	1,950	25	3,750	1:1.92	0.52
						4/ 6	10,000	6	600	45	4,500	1:7.50	0.13
11	L. S.	5 yrs.	Pleurisy with effusion	Animal inoculation	Living	2/19	10,000	14	1,400	16	1,600	1:1.14	0.87
						2/26	12,000	10	1,200	12	1,440	1:1.20	0.83
12	E. B.	8 yrs.	Inguinal adenitis	Biopsy	Living	3/ 9	12,000	17	2,040	33	3,960	1:1.94	0.52
						3/23	9,000	10	900	47	4,230	1:4.70	0.21
						3/27	8,500	2	170	43	3,655	1:21.50	0.05

TABLE 2.—*Group 2—Clinically Doubtful Cases of Tuberculosis*

Case	Name	Age	Clinical Observations	Tuberculin	Roentgenogram	Date	White Blood Cells	Monocytes		Lymphocytes		Comparison Monocyte-Lymphocyte	
								Per Cent	Total	Per Cent	Total	Ratio	Per Cent
13	U. D.	1 yr.	Blood in stools; lungs clear; spleen palpable	0.1 mg. negative	Diffuse infiltration	12/ 2	17,000	8	1,360	40	6,800	1:5.0	0.20
						12/15	15,000	10	1,500	32	4,800	1:3.2	0.31
						1/ 7	12,000	8	960	56	6,720	1:7.0	0.14
14	J. W.	7½ mos.	Cough; indefinite pulmonary signs; spleen palpable	Negative, 0.1 mg. negative	Diffuse infiltration	1/13	16,000	12	1,920	33	5,280	1:2.75	0.36
						1/16	15,000	15	2,250	30	4,500	1:2.0	0.50
						1/21	14,500	10	1,450	39	5,855	1:3.9	0.26
						1/25	12,000	10	1,200	42	5,040	1:4.0	0.24
15	M. G.	13 mos.	Fever; cough; consolidation of upper part of left lung; loss in weight	0.1 mg. 0, negative mg.	Diffuse infiltration	1/18	24,000	2	480	23	5,520	1:11.5	0.09
						2/ 2	32,000	12	3,840	45	14,400	1:3.75	0.27
						2/ 5	16,000	14	2,240	34	5,440	1:2.43	0.41
						2/10	15,000	8	1,200	36	5,400	1:4.5	0.24
16	H. R.	3½ yrs.	Indefinite pulmonary signs	0.1 mg. 0, 0.2 mg. positive	Diffuse infiltration	11/17	16,000	27	4,320	32	5,120	1:1.2	0.84
						11/22	10,000	20	2,000	40	4,000	1:2.0	0.50
						12/ 8	10,000	8	800	50	5,000	1:6.25	0.16
						12/24	12,000	6	720	67	8,040	1:11.2	0.09
						3/30	15,000	8	1,200	56	8,400	1:7.0	0.14
17	C. G.	6 mos.	Consolidation of upper part of left lung; irregular fever; loss in weight	0.1 mg. negative	Diffuse infiltration	1/22	16,000	8	1,280	35	5,600	1:4.38	0.23
						2/ 5	15,000	12	1,800	30	4,500	1:2.5	0.40
						3/26	10,000	6	600	42	4,200	1:7.0	0.14

age groups, the average of figures given by Griffith,[5] Lucas,[6] Rogers [4] and the figures obtained by ourselves. The highest values of normal for percentage and total number of monocytes were taken in estimating these figures. Therefore, values above the average were regarded as significant in this study (table 3).

Study of the cases presented in group 1 shows that they fall into three fairly definite types, according to the activity of the process, judged by both clinical signs and observations on the blood. Thus, the first eight cases are those of patients with active miliary or generalized tuberculosis which progressed rapidly to a fatal termination. In each of these cases (except case 7; this patient was discharged as soon as diagnosis was made), it will be seen that the percentage and absolute number of monocytes rose steadily, the lymphocytes fell, and the monocyte-lymphocyte ratio increased to a figure far above normal. In cases 9, 10 and 12 the patients had active tuberculosis in which healing or retrogression of the process occurred. Here, the earlier studies revealed a high monocyte count, a low lymphocyte count and, therefore, a high monocyte-

TABLE 3.—*Estimated Normal Figures*

Age	White Blood Cells	Monocyte		Lymphocyte		Monocyte-Lymphocyte Ratio
		Per Cent	Total	Per Cent	Total	
6 months	12,000	5	600	50	6,000	1:10
6 months to 1 year	11,000	6	660	44	4,840	1:7.3
1 to 4 years	9,000	8	720	32	2,880	1:4
4 to 12 years	9,000	8	720	27	2,430	1:3.4
Adults	8,000	7	560	24	1,920	1:3.4 1:3.3

lymphocyte ratio. As healing occurred, the blood picture showed a reversal of these observations, that is, the number of monocytes fell, the number of lymphocytes rose, and the ratio fell rapidly. At discharge, each of these patients showed a low monocyte count and a lymphocyte count well above normal. Case 11 was that of a patient in whom the process remained active throughout the period of observation (from two to three weeks). The monocytes remained increased, the number of lymphocytes continued low and the ratio was constantly high.

A summary of these observations shows that the activity of the tuberculous process in the twelve infants and children in group 1 was reflected in the peripheral blood by a relative and absolute increase or decrease in the number of monocytes, a corresponding decrease or increase in the number of lymphocytes and the appearance of modified monocytes and

5. Griffith, J. P. C.: Diseases of Infants and Children, Philadelphia, W. B. Saunders Company, 1921.

6. Lucas, W. P., and Washburn, A. H.: Diseases of the Blood and Blood Building Organs, Clinical Pediatrics, New York, D. Appleton & Company, 1928, vol. 11, p. 38.

TABLE 4.—*Changes Observed in the Peripheral Blood in Case 2**

Date	White Blood Cells	Differential Count: Polymorphonuclears	Differential Count: Lymphocytes	Differential Count: Mononuclears	Total Mononuclears	Total Lymphocytes	Comparison Monocyte:Lymphocyte: Ratio	Comparison Monocyte:Lymphocyte: Per Cent
Normal	12,000	45	50	5	600	6,000	1:10.0	0.10
1/13	9,000	56	36	8	720	3,240	1: 4.5	0.22
1/21	9,000	60	26	14	1,260	2,340	1: 1.9	0.53
1/24	9,000	68	18	14	1,260	1,620	1: 1.3	0.75
1/27	10,000	72	15	13	1,300	1,500	1: 1.2	0.83
1/29	12,000	78	9	13	1,560	1,080	1: 0.7	1.43

* G. C., aged 3 months, was admitted with acute miliary tuberculosis. Death occurred three weeks later. Necropsy revealed extensive miliary tuberculosis; the meninges were not involved.

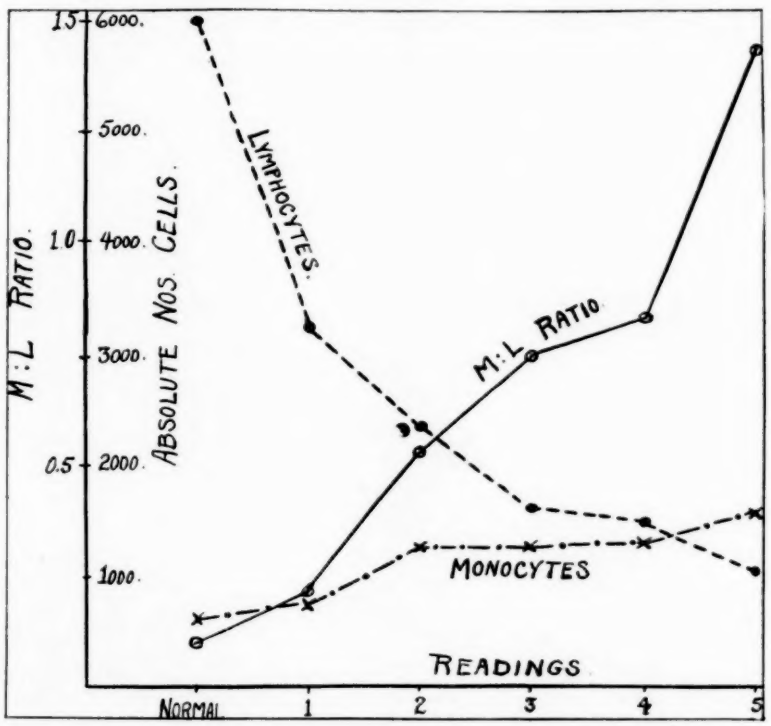

Chart 1 (case 2).—Observations on blood cells in a case of miliary tuberculosis; the average time interval was three days, although it varied from two to six days.

TABLE 5.—*Changes Observed in the Peripheral Blood in Case 3**

Date	White Blood Cells	Differential Count: Polymorphonuclears	Differential Count: Lymphocytes	Differential Count: Monocytes	Total Mononuclears	Total Lymphocytes	Comparison Monocyte:Lymphocyte: Ratio	Comparison Monocyte:Lymphocyte: Per Cent
Normal	12,000	45	50	5	600	6,000	1:10.0	0.10
2/27	20,000	75	20	5	1,000	4,000	1: 4.0	0.25
3/ 5	18,000	72	21	7	1,260	3,780	1: 3.0	0.33
3/ 9	20,000	70	14	16	3,200	2,800	1: 0.88	1.15
3/10	20,000	61	17	22	4,400	3,400	1: 0.77	1.30
3/14	20,000	77	9	14	2,800	1,800	1: 0.64	1.56
3/15	20,000	80	6	14	2,800	1,200	1: 0.43	2.33
3/19	25,000	81	6	12	3,000	1,500	1: 0.5	2.0
3/23	37,000	88	4	8	2,960	1,480	1: 0.5	2.0

* R. S., aged 4 months, was admitted with acute miliary tuberculosis and meningitis. Death occurred four weeks later. Necropsy revealed extensive miliary tuberculosis, involving the meninges.

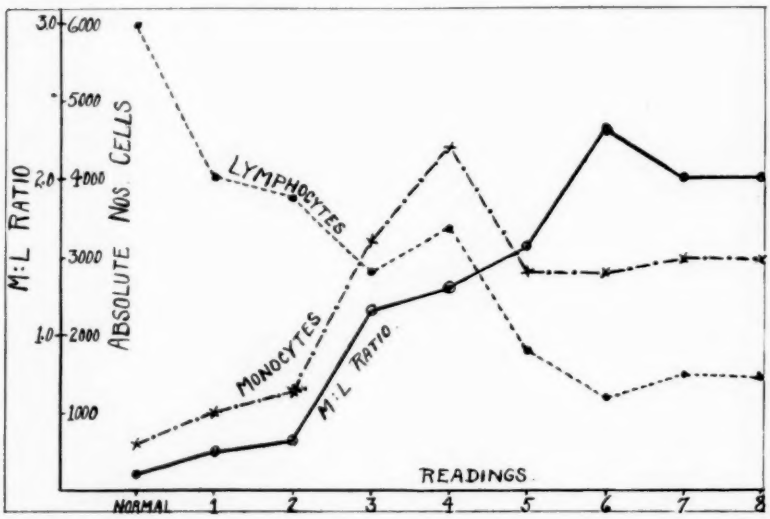

Chart 2 (case 3).—Observations on blood cells in a case of miliary tuberculosis with meningitis; the average time interval was three days, although it varied from two to six days.

TABLE 6.—*Changes Observed in the Peripheral Blood in Case 9**

Date	White Blood Cells	Differential Count: Polymorphonuclears	Differential Count: Lymphocytes	Differential Count: Monocytes	Total Monocytes	Total Lymphocytes	Comparison Monocyte:Lymphocyte: Ratio	Comparison Monocyte:Lymphocyte: Per Cent
Normal	9,000	65	27	8	720	2,430	1: 3.4	0.29
11/ 4	9,000	80	8	12	1,080	720	1: 0.67	1.50
11/ 9	10,000	76	10	14	1,400	1,000	1: 0.71	1.41
11/14	12,000	75	9	16	1,920	1,080	1: 0.56	1.80
			Operation					
11/20	14,000	70	21	9	1,260	2,940	1: 2.33	0.43
11/25	10,000	65	30	5	500	3,000	1: 6.0	0.17
12/ 2	10,000	60	38	2	200	3,800	1:19.0	0.05

* E. F., aged 9½ years, was admitted with masses in the abdomen. Laparotomy and biopsy of the gland revealed tuberculous peritonitis. There was a marked improvement during the following month.

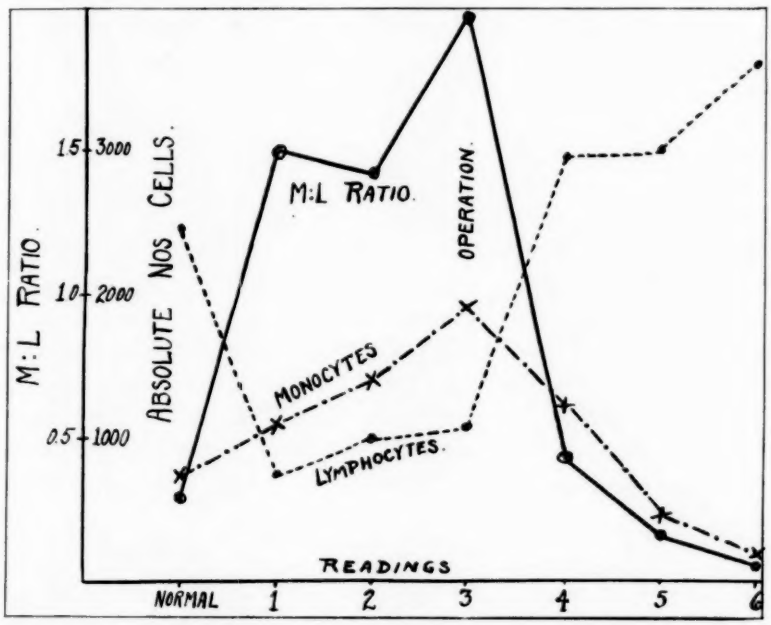

Chart 3 (case 9).—Observations on blood cells in a case of tuberculosis peritonitis; the time interval was three days, although it varied from two to six days. Between readings three and four, when the most marked changes had occurred, six days had elapsed.

epithelioid cells in the blood. As examples of the changes observed in the peripheral blood in active tuberculosis, a description of three cases is given in detail (cases 2, 3 and 9;[7] tables 4, 5 and 6; charts 1, 2 and 3). These results confirm the experimental studies of Cunningham, Sabin, Sugiyama and Kindwall, and the work of Cunningham and Tompkins, Rogers and others on tuberculosis in man.

As previously stated, we were unable to substantiate definitely by the usual methods the diagnosis of tuberculosis in the cases in group 2. The changes in the blood, however, suggest strongly the presence of infection with the tubercle bacillus, as they are similar to the observations in the proved cases of tuberculosis in group 1. As table 2 shows, the patients in cases 13 and 16 improved during the period of observation and were discharged in much better condition and are doing well at present. In cases 14, 15 and 17, the process remained active throughout the period of study, and the children were discharged to institutions for further care as patients suspected of having tuberculosis.

At the same time that the supravital stains were made, and from the same puncture wound, blood was taken for fixed smears. They were stained by the method of Wright. An unusual number of abnormal mononuclear cells was found in each of the seventeen patients. We are inclined to believe that these abnormal cells represent modified monocytes and epithelioid cells as they appear in fixed smears. Our reasons for this view are based on the fact that the percentage parallels closely the percentage of modified monocytes and epithelioid cells in the supravital stains (taken at the same time). Also, they have different reactions to various stains when compared with the other large mononuclear cells—the clasmatocyte. The exact identification of these cells in fixed smear must be deferred until further studies have been made.

The question naturally arises as to the significance of these changes in the blood stream in the diagnosis and prognosis of tuberculosis. In regard to diagnosis, reference to the following case will be of interest.

REPORT OF CASE

A girl, aged 9 years (case 8), was admitted to the hospital in August, 1927, with a history of cough, fever, loss in weight and epigastric pain. The diagnosis of tuberculosis was considered, but with an equivocal roentgenogram of the lungs and a negative reaction to tuberculin, even with 2 mg. of tuberculin, a positive diagnosis was not made. Roentgenograms of the gastro-intestinal tract revealed a duodenal ulcer. Treatment with the Sippy diet brought improvement, and the

7. Hereafter, in referring to the increased monocyte-lymphocyte ratio as being significant of tuberculosis, we include as well the presence of modified monocytes and epithelioid cells. The occurrence of such cells is essential, as an increased monocyte-lymphocyte ratio may be found in other diseases. We have found that the ratio increased in congenital syphilis and in acrodynia, and an increased ratio has been found in malta fever, pneumonia and infectious jaundice.

patient was discharged. Eight months later, she returned with the reappearance of the former symptoms. On admission, blood studies showed a monocyte-lymphocyte ratio of 1 : 1.2 and the presence of epithelioid cells. The diagnosis of tuberculosis was made on these observations, even though the reaction remained negative with 4 mg. of tuberculin. Twelve days after admission, tubercle bacilli were recovered in the sputum and feces. The patient continued to run a down hill course, and she finally died one month after admission to the hospital. Necropsy showed an extensive generalized tuberculosis.

As to prognosis, eight patients (cases 1 to 8) with a steadily increasing monocyte-lymphocyte ratio, died. In three patients (cases 9, 10 and 12), after an initial rise in the monocyte-lymphocyte ratio, the ratio was reversed and approached the normal ratio for the age. As the number of lymphocytes rose, it was noticed that the large young lymphocytes predominated. The changes in the blood preceded and pointed to the general improvement in the patient's condition. In one patient (case 11), the monocyte-lymphocyte ratio has remained increased. As continued studies have not shown significant changes, we believe that the tuberculous process, although active, is not advancing.

CONCLUSIONS

1. The degree of activity in tuberculosis is reflected in the peripheral blood of infants and of children.

2. A high monocyte-lymphocyte ratio and the presence of epithelioid cells usually mean an active tuberculous infection.

3. An increasing monocyte-lymphocyte ratio and the persistence of a high absolute monocyte count signify extension of the process.

4. Reversal of the ratio (a fall in monocytes and an increase in lymphocytes) denotes healing lesions.

5. In cases in which the diagnosis is questionable, a study of the blood by the supravital technic may lead to a correct diagnosis.

6. When the diagnosis is established, supravital studies of the blood may be of prognostic value in indicating whether the lesion is progressing or undergoing regression.

ACID-BASE METABOLISM

EFFECTS OF ADMINISTRATION OF SALT AND OF RESTRICTION OF WATER *

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In 1906, Meyer [1] observed a rise of temperature in infants following the feeding of casein of human milk added to whey of cow's milk. This observation stimulated further study of the factors inducing fever in infants, when a variety of substances was given either enterally or parenterally. Finkelstein [2] concluded that the fever which accompanied certain cases of severe diarrhea (alimentary intoxication) was not the result of infection but was due to the sugar present in the feeding, since frequently after the withdrawal of lactose from the food, the temperature became normal. Further observations, particularly those of Moro,[3] pointed to the fact that salts and protein, especially the latter, were of even greater importance than sugar in the production of fever. Later, the pyrogenic effect of an inadequate water intake was appreciated. Marriott [4] emphasized the great importance of the water deficit in the pathogenesis of "alimentary intoxication" and introduced the term "anhydremia." The other symptoms were considered secondary to an insufficient water supply or increased water loss from the body. Finkelstein [5] observed that fever resulted in about 10 per cent of the cases, when the daily water intake was less than 50 or 60 Gm. per kilogram of body weight. As the result of these experimental observations, he concluded, in a summary of the pathogenesis of alimentary fever, that an increase of the osmotically active constituents of the body fluids frequently played an

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1. Meyer, L. F.: Beitrag zur Kenntnis der Unterschiede zwischen Frauen-und Kuhmilchernährung, Monatschr. f. Kinderh. **5**:361, 1906.

2. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, ed. 3, 1925, p. 266.

3. Hirsch, A., and Moro, E.: Untersuchungen über alimentäres Fieber, Jahrb. f. Kinderh. **86**:341, 1917.

4. Marriott, McKim: Some Phases of the Pathology of Nutrition in Infancy, The Harvey Lectures, Philadelphia, J. B. Lippincott Company, 1920-1921.

5. Finkelstein (footnote 2, p. 269).

important rôle, presumably by causing damage to the liver and permitting intoxication by protein split products from the intestinal tract. On the other hand, Marriott,[4] referring to the experimental work of Balcar, Sansum and Woodyatt,[6] thought that the lack of water alone may have been responsible for the symptoms observed and that it was not necessary to look for some toxic product.

Meyer [7] and Schloss [8] concluded that the increase of the osmotic concentration of the body fluids was not the only factor in the production of fever, since all substances with equal osmotic concentration did not produce fever. Thus sodium salts, particularly the chloride, were found to produce a rise and calcium salts a fall in temperature, while potassium salts gave variable results. Recently, Rietschel [9] advanced the idea that sodium chloride had an effect similar to that of the specific dynamic action of protein in stimulating metabolism.

In the presence of an increased plasma bicarbonate (alkalosis), the administration of sodium chloride is known to lead to the excretion of bicarbonate into the urine.[10] In discussing the pathogenesis of anhydremic acidosis, Hartmann [11] concluded that the administration of salt solution was a factor in preventing the restoration of plasma bicarbonate and was therefore contraindicated.

Since the parenteral administration of saline solution has become a frequent procedure in the treatment for anhydremia, it has seemed desirable to study the effects of the administration of sodium chloride on the composition of the plasma and urine of normal infants, from the standpoint of the acid-base balance and total osmolar concentration. This was done. The effect of feeding concentrated food mixtures with water restriction was also studied.

Healthy infants were selected. Six of these received daily doses of from 6 to 10 Gm. of sodium chloride distributed equally in the feedings over a period of from one to four days. Water was not restricted in

6. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and the Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

7. Meyer, L. F.: Die Bedeutung der Mineralsalze bei den Ernährungsstörungen des Säuglings, Jahrb. f. Kinderh. **71**:1, 1910.

8. Schloss, E.: Zur Biologischen Wirkung der Salze, Mittlg. I.: Einfluss der Salze auf die Körpertemperatur, Biochem. Ztschr. **18**:14, 1909.

9. Rietschel, H.: Zur Frage des Kochsalzfiebers, Monatschr. f. Kinderh. **37**:307, 1927.

10. Hartmann, A. F., and Smyth, F. S.: Chemical Changes in the Body Occurring as a Result of Vomiting, Am. J. Dis. Child. **32**:1 (July) 1926.

11. Hartmann (footnote 10). Hartmann, A. F.: Chemical Changes Occurring in the Body as a Result of Certain Diseases, Am. J. Dis. Child. **35**:557 (April) 1928.

these cases. In one instance a very concentrated formula was substituted for the usual one, and additional water was entirely restricted.

METHODS

In the studies of the blood, methods similar to those used by Hartmann [11] were employed. All determinations were done on serum. In most instances, the total fixed base was determined by the method of Stadie and Ross.[12] In a few instances, Van Slyke's [13] method was used.

The urine was collected under oil. The acid-base balance was calculated according to the scheme of Gamble [14] by determining the total fixed base, ammonia and titrable acidity on one hand and on the other, all the principal fixed acids and the organic acids. All the acid values are expressed in milliequivalents of monovalent base at the p_H of the urine. The total base was determined by the method of Stadie and Ross [12] without removal of phosphate, and correction was not made for the latter (Hartmann and Darrow [15]).

Besides the ammonia quotient, György's [16] total acid coefficient $\frac{A + NH_3}{N} \times 100$ was calculated. In this formula, A means titrable acidity. All values are expressed in terms of cubic centimeters of tenth normal acid. In the absence of determinations of the fixed base, the latter quotient was of some value in indicating the amount of fixed acid excreted not bound to fixed base, in relation to the excretion of nitrogen.

THE EFFECT OF ADMINISTRATION OF SODIUM CHLORIDE

Changes in the Plasma.—As can be noted from table 1, an increase of BCl of the serum from 6 to 15 per cent occurred following the addition of salt to the diet. $BHCO_3$, however, diminished in four instances (2, 3, 4 and 6), while in two instances (1 and 5) it remained unchanged. The bicarbonate decreased 17.3 per cent in cases 2 and 5, and 6.5 per cent and 7 per cent, respectively, in cases 3 and 4. Lactic and phosphoric acid did not show remarkable changes except in one instance (case 2), in which lactic acid was increased to a considerable amount over its value in the first period. Serum protein showed its greatest change in case 2, being increased by 17.7 per cent. Concentration of the plasma also

12. Stadie, W. C., and Ross, E. C.: A Micro Method for the Determination of Base in Blood and Serum and other Biological Material, J. Biol. Chem. **65**:735, 1925.

13. Van Slyke, D. D.; Hiller, A., and Berthelsen, K. C.: A Gasometric Micro-Method for Determination of Iodates and Sulfates and Its Application to the Estimation of Total Base in Blood Serum, J. Biol. Chem. **74**:659, 1927.

14. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: The Metabolism of Fixed Base During Fasting, J. Biol. Chem. **57**:633, 1923. Gamble, J. L., and Hamilton, B.: Bull. Johns Hopkins Hosp. **41**:389, 1927.

15. Hartmann, A. F., and Darrow, D.: To be published.

16. György, P.: Zur Frage der Säureausscheidung im Urin, Ztschr. f. d. ges. Exper. Med. **43**:443, 1924.

TABLE 1.—*Results of the Chemical Examination of the Blood of Infants After the Administration of Sodium Chloride (Cases 1 to 6) and Concentrated Food (Case 7)*

Case	Period	p_H	Chloride	Bicarbonate	Phosphate	Lactate	Protein, Gm. per 100 Cc.	Total Acid*	Total Base	Dextrose	Non-protein Nitrogen	Calculated	Observed	Comment
			Base-Acid Equivalent Cc. Tenth Normal					Cc. Tenth Normal per 100 Cc.		Mg. per 100 Cc.		Osmolar Millimols		
1	Fore	7.45	100.0	23.3	3.0	2.0	6.12	143.2	127.0	91	30	297.4	...	Food: 900 cc. whole lactic acid milk; 6 Gm. sodium chloride; highest temperature, 39 C.; weight dropped 300 Gm. on day of experiment
	After	7.42	111.1	23.5	3.0	2.0	6.12	154.0	136.0	94	29	318.3		
2	Fore	7.39	105.0	21.4	2.8	0.2	6.12	142.9	147.0	87	20	286.7	309	Food: 900 cc. whole lactic acid milk; 10 Gm. sodium chloride daily during four days of experiment; highest temperature, 38.5 C.; weight unchanged
	After	7.33	114.0	17.7	3.1	4.1	7.20	153.3	156.0	117	23	311.8	312	
3	Fore	7.37	101.0	21.4	1.7	3.0	6.77	141.0	135.0	79	24	275.9	304	Food: 1,200 cc. whole lactic acid milk; 10 Gm. sodium chloride; highest temperature, 39 C.; weight dropped 200 Gm.
	After	7.37	110.0	19.9	1.7	2.2	6.55	147.2	142.0	109	22	291.0	308	
4	Fore	7.43	101.0	22.8	3.8	1.7	7.85	143.3	145.0	101	34	277.5	...	Food: 900 cc. whole lactic acid milk; 10 Gm. sodium chloride daily during three days; highest temperature, 37.8 C.; gain in weight, 270 Gm.
	After	7.42	115.0	21.3	3.5	2.7	7.42	155.7	147.0	98	30	301.0		
5	Fore	7.42	95.0	22.7	4.1	4.0	6.34	137.3	142.0	96	31	290.8	...	Food: 810 cc. whole lactic acid milk; 6 Gm. sodium chloride; highest temperature, 39 C.; weight unchanged
	After	7.42	104.0	22.7	3.3	2.1	5.68	142.2	146.0	93	26	298.1		
6	Fore	7.42	102.0	22.6	3.4	2.0	5.47	136.8	144.0	63	34	286.6	...	Food: 810 cc. whole lactic acid milk; weight unchanged; 8 Gm. sodium chloride daily during three days of experiment; highest temperature, 38.5 C.
	After	7.37	108.0	18.7	3.7	3.4	5.90	144.0	144.0	76	34	300.9		
7	Fore	7.47	98.0	23.9	2.9	3.0	6.98	140.5	135.0	80	24	293.0	...	300 cc. of water + 900 cc. of whole lactic acid milk = 900 calories; 300 Gm. Dryco + 70 cc. of Karo syrup in 830 cc. of water
	After	7.42	126.0	19.7	3.6	4.0	8.06	167.7	161.0	...	38	356.3	356.5	

* This value includes protein as calculated by Van Slyke's formula.

occurred in case 6, as indicated by a 7.3 per cent increase of protein. The other cases (3, 4 and 5) showed plasma dilution as indicated by a fall in the protein concentration amounting to 3.2, 5.7 and 10.4 per cent, respectively. In case 1, the serum protein concentration remained unchanged. The p_H of the serum showed a shift toward the acid side in cases, 2, 5 and 6. In the other cases, the p_H remained constant.

In all instances the sum of the five principal normal acids determined increased appreciably. A parallel increase in total base [17] was noted, indicating that a change in undetermined acid had not occurred. The calculated electrolyte osmolar concentration as well as the total osmolar concentration increased in all instances. In two instances (2 and 3) the actual freezing point of the serum was determined, and corresponded well with the calculated values. In four instances there occurred a slight diminution of nonprotein nitrogen (1, 3, 4 and 5). In one instance (6) it remained unchanged, and in one instance (2) it increased slightly.

Urine.—The most marked changes were shown in cases 2 and 3. In both of these, administration of salt was followed by a relative increase in excretion of fixed base over fixed acid. In other words, there was an increased excretion of base bicarbonate in the urine at the expense of the bicarbonate of the blood. There was naturally an increase in urinary chloride, but this did not equal the intake. Coincident with the increased excretion of bicarbonate, the hydrogen ion concentration of the urines shifted toward the alkaline side. In case 2, there was slight fever and moderately increased excretion of nitrogen. In case 3, in which there was considerable fever, a 53 per cent increase in excretion of urinary nitrogen occurred, indicating a definite rise in protein metabolism. As fever with increased protein destruction is known to lead to a reduction in cell volume, one would naturally expect an increased excretion of cell water and cell electrolyte, and this occurred in my cases. This corresponds to the observations of Gamble [18] on fasting children. In contradistinction to Gamble's observations, however, the urines of our patients became more alkaline, due to an increased excretion of bicarbonate. The changes in the urine are in agreement with György's [17] observations in his study of the excretion of acid in infants after they were fed salt.

In cases 1 and 4 in which our data are not so complete, the changes observed were similar in nature to those in cases 2 and 3.

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17. In a number of instances, total acid exceeded total base, due, I think, to errors in the determination of the latter. I believe that such errors are consistent, permitting conclusions concerning relative values in the same experiment.

18. Gamble (footnote 15, first reference).

THE EFFECTS OF CONCENTRATED FEEDING AND RESTRICTION OF WATER

An infant, aged 5½ months (case 7), receiving a usual formula of whole lactic acid milk with the addition of 10 per cent sugar in the form of corn syrup (900 cc. equivalent to 900 calories) together with 300 cc. of water, was changed to a formula consisting of 300 Gm. of Dryco and 70 cc. of corn syrup in 870 cc. of water (equivalent to 1,500 calories). Additional water was not offered.

Within four hours, a rise in temperature occurred. By the end of twenty hours, the temperature had reached 41 C. (105.8 F.). At this time the infant appeared decidedly "toxic"; the eyes were dull and somewhat sunken, the skin was gray, dry and inelastic, the breathing was slightly hyperpneic, and there was marked restlessness.

Shortly after this high temperature had occurred, the stools became loose and during the next twenty-four hours totaled ten in number, as contrasted to the three during the previous twenty-four hours. The administration of the concentrated food was then discontinued, water was given, and later the usual lactic acid milk formula was resumed. The symptoms subsided rapidly, the temperature became normal in twenty hours, and to all appearances the child was again well. During the period of concentrated feeding, the body weight had dropped 450 Gm., approximately half of which was accounted for by increased urinary excretion.

Recently, similar experiments have been reported by Schiff [19] in which anhydremia was produced by feeding a high protein diet with restriction of water.

Changes in the Plasma.—At the time of the highest temperature, when the symptoms of dehydration and toxicity were most marked, blood was secured for chemical study (table 1). The blood was concentrated, as shown by a 13.4 per cent increase in serum protein. Concentration of phosphoric and lactic acid and nonprotein nitrogen was also noted. An even greater concentration of chlorides occurred (28.5 per cent). Bicarbonate, on the other hand, was not concentrated but was reduced by 17.5 per cent. With this reduction in bicarbonate, the p_H of the serum dropped from 7.47 to 7.42. Due chiefly to the chloride increase, the total acid increased by 19.3 per cent and was accompanied by a 19.3 per cent increase in base, indicating that a change in undetermined acid had not occurred.

The total theoretical osmolar concentration increased from 293 to 356.3 millimols. The observed freezing point of the serum corresponding to the latter theoretical osmolar concentration indicated a total of 356.5 osmolar millimols.

Urine.—An appreciable rise in excretion of bicarbonate did not take place in the urine, and corresponding to this the p_H of the urine was unchanged. The output of nitrogen and chloride increased in keeping

19. Schiff, E.; Bayer, W., and Fukuyama, M.: Zur Pathogenes der Ernährungsstoerungen beim Saeugling: XI. Das Saeurebasengleichgewicht bei experimenteller Exsikkose, Jahrb. f. Kinderh. **119**:61, 1928.

TABLE 2.—*Results of the Chemical Examination of the Urine of Infants After the Administration of Sodium Chloride (Cases 1 to 4) and Concentrated Food (Case 7)* *

Case	Period	Volume, Cc.	p_H	Chloride	Bicarbonate	Phosphate	Sulphate	Organic Acid	Fixed Base	Ammonia	Titrable Acidity	Total Acid	Total Base	Nitrogen	Ammonia Coefficient	György's Coefficient
				Base-Acid Equivalent, Cc. Tenth Normal					Cc. Tenth Normal							
1	Three days before experiment.....	346	5.80	255	21	...	...	...	.....	131	92	.....	.....	1,639	8.3	14.2
	Day of experiment.....	330	6.05	709	30	...	...	...	.....	90	97	.....	.....	2,004	4.5	9.3
	Two days after experiment.....	185	7.35	319	130	...	...	...	.....	207	42	.....	.....	1,286	16.2	19.6
2	Two days before experiment.....	365	6.75	298	31	108	80	59	425	93	45	576	563	1,064	8.7	11.8
	Four days of experiment.....	343	6.90	839	47	115	68	52	1,022	78	40	1,121	1,140	1,231	6.4	9.6
	Three days after experiment.....	193	6.40	256	17	115	66	39	362	102	73	493	537	1,214	8.4	14.4
3	Three days before experiment.....	230	6.75	170	18	128	83	58	296	100	53	457	449	1,660	6.0	9.3
	First day of experiment.....	530	7.00	1,219	90	221	135	207	1,601	143	66	1,872	1,810	2,544	5.6	8.2
	Three days after experiment.....	223	7.10	320	48	160	92	66	500	144	43	686	687	1,855	7.7	10.0
4	Three days before experiment.....	330	6.35	307	45	...	...	...	.....	146	167	.....	.....	1,402	9.7	21.0
	Three days of experiment.....	310	6.60	916	51	...	...	...	.....	99	120	.....	.....	1,261	7.5	17.0
	Two days after experiment.....	405	6.75	650	86	...	...	...	.....	165.5	134	.....	.....	1,570	10.45	18.5
7	Four days before experiment.....	305	5.9	273	4	...	...	...	.....	159	160	.....	.....	1,857	8.6	17.2
	First day of experiment.....	480	5.95	662	8.6	...	...	...	.....	99	233	.....	.....	4,640	2.1	7.2
	Four days after experiment.....	300	6.0	306	5.4	...	...	...	.....	101	143	.....	.....	1,855	5.4	13.2

* The values represent the twenty-four hour average.

with the higher intake. The decrease in ammonia was approximately balanced by increase in the titrable acidity. Both the ammonia and the total acid coefficients decreased.

SUMMARY

A study was made of the effects of the administration of sodium chloride and of restriction of water on the total metabolism and the acid-base equilibrium of the body.

The administration of sodium chloride to infants in addition to a regular diet and in the absence of restriction of water resulted in: (1) an increase in the chloride concentration of the plasma; (2) usually a moderate reduction of plasma bicarbonate; (3) a tendency for the reaction of the plasma to shift toward the acid side; (4) changes in both directions in the water content of the plasma as shown by protein concentration; (5) a constant increase in excretion of bicarbonate in the urine, with a shift in reaction toward alkalinity; (6) a relative increase in excretion of fixed base over fixed acid; (7) a decrease in György's coefficient in the urine, and (8) a slight or moderate febrile reaction in most instances.

The feeding of a concentrated food with restriction of water produces the same changes in metabolism as did the administration of sodium chloride. The blood concentration, however, was marked and fever was high. Symptoms characteristic of alimentary intoxication were observed.

The results indicate the possible danger of the indiscriminate administration of salt solutions to infants suffering from anhydremia. The effect of such administration may be to increase the degree of acidosis and to prevent the restoration of a normal acid-base equilibrium.

THE RÔLE OF INFECTION IN RHEUMATIC CHILDREN *

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AND
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ST. LOUIS

This study was undertaken in order to find how far the routine supervision of rheumatic children in hospitals and clinics affects the tendency to recurrence of rheumatic manifestations. One hundred and fifty members of the Children's Heart Clinic of Washington University were included in this study. Cases were excluded in which the early history was inadequate or in which obvious rheumatic heart disease was present without a history of exudative signs, as it was on such signs that the study was based. The care in the clinic has been directed chiefly toward the improvement of the general health, whether in the child's own home or at Ridge Farm convalescent home, and has included measures directed toward removal of foci of infection.

The periods over which the children have been watched vary between nine months and eleven years; 116 have been followed for more than one year and seventy-three for more than two years. All of the patients have been seen within the last three months, and their status as to recurrences of rheumatism and coincident infections of the upper respiratory tract was noted. The sexes were equally represented, seventy-four being males and seventy-six females. Ten colored children were included in this study. The small number of colored children may be explained by the fact that a larger number failed to attend the clinic with sufficient regularity to be included in this study.

AGE INCIDENCE AND SEASONAL INCIDENCE

The Age Incidence in First Attacks.—The age incidence was found to be in accordance with the figures of other writers.[1] In none of the cases had the primary attack occurred when the patient was under 2 years of age, but from the age of 3 years the tendency to rheumatic fever increased rapidly, a maximum of first attacks between the ages

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1. Mackie, T. T.: Am. J. M. Sc. **172**:199, 1926.

of 10 and 12 years being noted (chart 1). After this the frequency of attacks dropped rapidly until in patients of 15 years of age first attacks were not noted. This diminution in the incidence of first attacks at the age of puberty is probably exaggerated as the number of rheumatic children seen between the ages of 14 and 16 is small, most of these patients being admitted to clinics for adults. Mackie's statistics show a more gradual diminution. The sharp peak in the incidence of rheumatism in childhood and the low figures for both the preschool and

Chart 1.—Observation of a series of cases showing the age incidence in first attacks of rheumatic fever.

the adolescent child point to the possibility of the infection being first acquired during the gregarious early school life of the child.

The Seasonal Incidence of Rheumatic Fever.—A study of the seasonal incidence of attacks of rheumatic fever and chorea corroborated the usual impression that the disease is most common in this country during the spring months (chart 2). This corresponds with the period of worst weather conditions and most frequent infections of the upper respiratory tract and is in contrast with similar studies made in England where the peak of incidence is during the late fall months, at which time cold and damp seem particularly prevalent.

THE ASSOCIATION OF INFECTIONS OF THE UPPER RESPIRATORY TRACT PRECEDING AND BETWEEN ATTACKS OF RHEUMATIC FEVER

A survey of the association of infections of the upper respiratory tract with the incidence of attacks of the disease and recurrences was made from two standpoints: (1) the number of attacks preceded by such infections, and (2) the incidence of such infections between attacks of rheumatic fever. It was found that in this group of 150 children, rheumatic fever or chorea had occurred 304 times, and definite information concerning the prodromal signs was noted in 261 instances. These are tabulated in table 1, in which it will be seen that colds and sore throats apparently precipitated 197 of the attacks—figures which con-

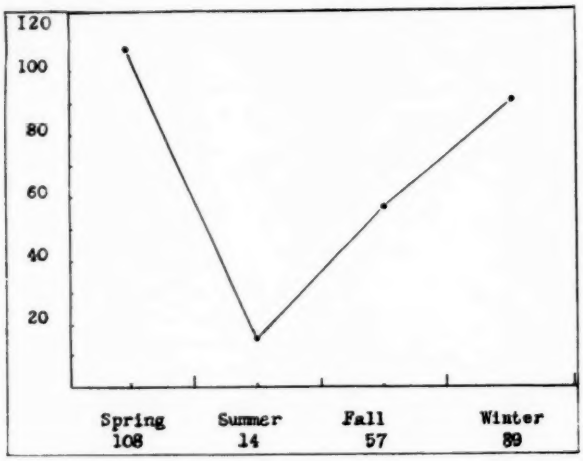

Chart 2.—The rôle of infection in rheumatic fever showing the seasonal incidence.

firm the general impression of the association of the acute infections of the upper respiratory tract with rheumatic fever.

Zymotic diseases and pyogenic infections preceded thirty-six attacks, while in twenty-eight instances an initial infection was denied. Studies of the occurrence of colds and sore throats in rheumatic subjects without reference to the acute attacks of rheumatism show the increased incidence of such infections. In ninety-five of the one hundred and fifty subjects infections of the upper respiratory tract were extremely frequent. Fifteen subjects gave a history of fairly frequent or occasional infections and thirty-eight did not have infections of the upper respiratory tract in the absence of rheumatic fever. Of this last group, eighteen subjects reported that their acute rheumatic manifestations were always ushered in by an acute cold or by a sore throat. As considerable effort had been made to lower the incidence of colds in this group studied,

our figures are probably lower than the actual incidence of infections of the upper respiratory tract in subjects not treated for the rheumatic condition. They are, however, sufficiently high to point not only to the association of acute infections with the acute exudative symptoms of the rheumatic syndrome, but also to the marked susceptibility which rheumatic subjects show to such infections between attacks of rheumatic fever.

THE RÔLE OF TONSILLECTOMY IN RECURRENCES OF RHEUMATIC FEVER

Reports in the literature concerning the effects of tonsillectomy on recurrences of rheumatism in children have been contradictory.[2] Kaiser found that tonsillectomy performed for various reasons on a large group of children did not lessen the subsequent incidence of rheumatism.

TABLE 1.—*Attacks Associated with Colds and Sore Throats and Other Infections*

Total attacks preceded by frank tonsilitis or sore throat	98
Total attacks preceded by common colds	74
Total attacks preceded by both colds and sore throats	25
Total attacks preceded by other infections	36
Otitis media with sore throat	4
Otitis media without sore throat	5
Scarlet fever	6
Measles	6
Abscessed teeth	5
Tonsillectomy (after operation)	3
Pyelitis	2
Pneumonia	2
Bronchitis	1
Abscess of back	1
Appendicitis	1
Total attacks preceded by no obvious infection	28

Ingerman and Wilson,[3] working with rheumatic children, found that recurrences of rheumatic fever were as common in the group in which tonsillectomy had been performed as in the group of those not subjected to the operation. This has also been the experience of Poynton, Paterson and Spence[4] and other British workers. On the other hand, St. Lawrence[5] and Mackie,[1] on the basis of their good results, expressed the belief that tonsillectomy is one of the important measures in the care of rheumatic children; this has also been our experience. Reference to

2. Kaiser, A. D.: Effect of Tonsillectomy on General Health of 1,200 Children as Compared with an Even Number Not Operated On, J. A. M. A. **83**:33 (July 5) 1924.

3. Ingerman, E., and Wilson, M.: Rheumatism; Its Manifestations in Childhood Today; Tonsillectomy in Its Relation to Recurrence of Rheumatism, J. A. M. A. **82**:759 (March 8) 1924.

4. Poynton, F. J.; Paterson, D., and Spence, J. C.: Lancet **2**:1086 (Nov.) 1920.

5. St. Lawrence, W.: Effect of Tonsillectomy on Recurrence of Acute Rheumatic Fever and Chorea, J. A. M. A. **75**:1035 (Oct. 16) 1920.

table 2 will show that the highest total number of attacks per person occurred in those subjects on whom tonsillectomy was performed during the period of observation.

In this group of ninety-two subjects, a total of 200 attacks were recorded, slightly more than two per subject. Analysis of this shows, however, that the children averaged 1.53 attacks before tonsillectomy and 0.64 subsequently. As the average length of time the subjects were known to have rheumatism before tonsillectomy was thirty-five months, and the time observed subsequently was thirty-two months, it will be seen that great benefit was obtained from the standpoint of prevention. A rather high incidence of rheumatic fever in patients on whom tonsillectomy was performed before the first attack is thought to be evidence of the probable severity of early infections of the upper respiratory tract which necessitate tonsillectomy. The group in which tonsillectomy had not been performed consisted for the most part of children whose tonsils

TABLE 2.—*Rôle of Tonsillectomy in the Occurrence of Rheumatic Fever*

1.	Subjects tonsillectomized before first attack	18
	Attacks occurring in this group	36
	Attacks per subject	2
2.	Subjects not tonsillectomized	34
	Attacks occurring in this group	60
	Attacks per subject	1.76
3.	Subjects tonsillectomized during observation	92
	Attacks occurring in this group	200
	Attacks per subject before operation	1.53
	Attacks per subject after operation	0.64
4.	Subjects awaiting tonsillectomy	5
5.	Subjects with first attack following operation	1
	Total	150

gave little trouble; consequently, as would be expected, the incidence of rheumatic attacks in this group was low. A study of the marked disparity in the conclusions of the various authors cited as to the value of this operation reveals that St. Lawrence, Mackie and we have emphasized the necessity of caring for other foci of infection, and that since operation we have followed the cases intensively from that standpoint. Kaiser mentioned only that the children were examined three years after the tonsillectomy, but he did not note any attention which had been paid to them during the interval. Ingerman and Wilson,[3] although stating their routine care of such children, did not stress the fact that any special care was taken to prevent other infections of the upper respiratory tract. We have felt that this intensive follow-up care probably assists in producing the ultimate good results of the operation.

EFFECTS ON RECURRENCE OF CARE IN A CONVALESCENT HOME OR IN THE PATIENT'S OWN HOME

The Effects of Prolonged Care in a Convalescent Home on the Recurrence of Rheumatism.—A large number of the children seen in

the hospital and clinic with rheumatic manifestations were transferred to Ridge Farm convalescent home, the country department of the St. Louis Children's Hospital. Here they were kept for periods varying from about three to twenty-four months, during which time an effort was made by a trained social worker to adjust the home to the child's requirements. The occurrence of acute rheumatic manifestations at the convalescent home is extremely rare. Taking a total length of stay at the farm of 647 months, it was found that in 100 children, only seven attacks would occur, while 100 children of the same group at home for a similar length of time would have thirty-seven attacks. When, however, the figures for the number of attacks subsequent to the care received at the Ridge Farm are considered, a different aspect is presented. Table 3 shows that the incidence of recurrence after convalescent care is greater than the incidence in children who have not been admitted to the farm, but who have been cared for at home.

TABLE 3.—*Limitations of Convalescent Care in Rheumatic Fever*

Subjects of this study under observation for at least 24 months	65
Subjects in the Ridge Farm group	39
Subjects in control group not admitted to Ridge Farm	26
	Per Person
Total attacks before admission to Ridge Farm	1.49
Total attacks since admission to Ridge Farm	.74
Total attacks of control group at home before supervision	1.72
Total attacks of control group at home since supervision	.46
Attacks occurring at Ridge Farm in 85 children who had a total stay of 647 months, compared with the number of attacks occurring in an unselected group of 54 children of the Ridge Farm group who have been at home for the same period of 647 months.	
Total attacks in 85 subjects at Ridge Farm for 647 months	6
Total attacks in 54 subjects at home for 647 months	20
100 children at Ridge Farm will have 7 attacks; 100 children at home will have 37 attacks.	

As both groups are supervised in the home, the explanation of this difference seems obscure. In an effort to explain this difference, such factors as the length of time the two groups were observed, the inclusion of negro children in the control series and a possible difference in the severity of the original rheumatic manifestations in the two groups have been considered. It was found that the average time a patient of the Ridge Farm was observed after his return was 46.3 months, while the average time the control cases had been watched was 48 months. The cases of three negroes were included in the control group, but it was found that their inclusion made practically no difference in the number of recurrences. The question as to whether the severity of the rheumatic manifestations in the two classes differs is difficult to answer, as it is not certain that a severe rheumatic fever is more likely to be followed by a recurrence than a milder attack of the disease, and the cases of chorea were about equally divided in the two groups. We think that the groups were fairly comparable from this standpoint,

as well as from that of parental cooperation. As none of these possible factors actually could be held responsible for the disparity, we have felt that it is possible that children kept free from infections of the upper respiratory tract during their stay at a convalescent home may actually be more susceptible to such infections, with the attendant rheumatic manifestations, on their return to their usual life.

Effect of Care in the Home of Patients with Infections of the Upper Respiratory Tract on the Incidence of Recurrences.—The most encouraging figures in this survey were obtained from a study of subjects who were given intensive care directed toward the eradication of nasopharyngeal infections. Table 4 shows that 142 of the children could be grouped according to the condition of their nasopharynx on clinical examination.

TABLE 4.—*Results of Therapy Directed Toward Control of Infection in Nose and Throat*

1.	Total subjects without evidence of infection in nose and throat at any time		20
2.	Total subjects with evidence of infection only preceding and during attacks of rheumatic fever		32
3.	Total subjects with evidence of infection between and during attacks		90
	Total subjects of group 3 observed for 12 months or more	80	
	Total subjects of this group cooperating satisfactorily	58	
	(a) resulting in clean nasopharynx	40	
	Number of attacks in this group subsequent to supervision	4 or 10%	
	(b) not resulting in clean nasopharynx	18	
	Number of attacks in this group subsequent to supervision	3 or 16.6%	
	Total subjects in this group not cooperating satisfactorily		22
	Total in whom the nasopharynx spontaneously cleared up		2
	Number of attacks in this group subsequent to observation	1 or 50%	
	Total in whom the nasopharynx remained infected		20
	Number of attacks in this group	10 or 50%	

Groups 1 and 2 are not included in this analysis, as an infection was not noted during the intervals between attacks. Group 3 consisted of ninety children, also further divided according to whether the parents cooperated or not in carrying out the measures recommended. It will be seen that the percentage of recurrences varied directly with the care given and with the good results obtained. Only 10 per cent of the children of the cooperative group in whom the nasopharynx became reasonably clean had recurrences, as contrasted with 50 per cent of the noncooperative group in which the nasopharynx seemed infected throughout. It is realized here that cooperative parents are cooperative in many other ways than by following instructions for nasopharyngeal hygiene, and that the success which follows was probably not necessarily due to any one measure, but to the result of improvement in general hygiene. These clinical observations on the association of focal infections in the upper respiratory tract with rheumatic fever are not without experimental support. There is considerable reason to believe, on the

basis of work done by Swift [6] and his colleagues, that rheumatism is an allergic response to streptococci, and that in experimental animals a focal lesion is necessary in keeping up this condition of allergy. Additional evidence concerning the allergic process of rheumatism has recently been obtained in our own laboratory.[7] We feel that it is probable that a large group of the ordinary streptococci of the upper respiratory tract may be etiologic, and that the specific characteristics of the disease depend, not on a specific organism, but on a difference in the tissues of the rheumatic subjects. Based on these facts, we consider that the ordinary infections of the upper respiratory tract, including tonsillitis, which is often mild, and the common nasopharyngitis, are responsible in most cases for the initial attack and subsequent recrudescence of rheumatism. Tonsillectomy, although not a cure, is, if accompanied by the following measures, responsible for considerable improvement in the patient. It has been a policy of this clinic in recent years to advise tonsillectomy almost as a routine for all rheumatic subjects. The care of such children may be divided into general measures for the care of the child and local treatment directed toward foci of infection. The child may be treated in the convalescent home or in his own home with equal success. In either case, the home usually requires readjustment to allow the adoption of those hygienic measures which prevent the spread of common colds. Care in the convalescent home, although of value in establishing convalescence from an acute attack, would seem to be of no value in preventing further attacks unless it is prolonged indefinitely. More intensive measures to improve the environment of the child after discharge from the hospital may result in a true prevention of attacks. Colds and sore throats, however mild, are regarded as serious. The child is kept from school and in bed until the temperature is normal, and various nasal instillations and gargles are prescribed in the hope of shortening the course of the infection. Chronic infection in the nasopharynx is watched for carefully and treated with instillations and occasional irrigation of the nose with hypertonic saline solution; the latter seems most effective when considerable purulent discharge in the nasopharynx is present. When the nasal sinuses are involved, drainage may be effected with the use of these solutions combined with such preparations as ephedrine and mild antiseptics. Operative measures other than tonsillectomy and adenoidectomy have not been considered advisable in the majority of cases. Although it is not felt that dental infection plays an important rôle in

6. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Bacterial Allergy (Hyperergy) to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, J. A. M. A. **90**:906 (March 24) 1928.

7. Irvine-Jones, E. I. M.: Skin Sensitivity of Rheumatic Subjects to Streptococcus Filtrates and Its Relationship to Rheumatic Fever, to be published.

the occurrence of rheumatism, it has been our policy to secure adequate dental care for these children in order to decrease as much as possible the amount of oral infection.

CONCLUSIONS

1. Clinical and experimental evidence tends to show the close association of infections of the upper respiratory tract with the rheumatic syndrome.

2. Tonsillectomy, when followed by hygienic measures, general and local, is of value in decreasing the number of recurrences of rheumatic fever and chorea.

3. Care in a convalescent home is of immediate benefit to the child but does not seem to lessen recurrences after the child goes home.

4. In a group of ninety children with constant infection in the nasopharynx, the percentage of recurrences of rheumatic fever and chorea was paralleled by the degree of success obtained in combating the infection and improving the living conditions of the child.

EXPERIMENTAL STUDY OF THE ACID-BASE EQUILIBRIUM IN CHILDREN WITH IDIOPATHIC EPILEPSY *

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Of the various theories thus far advanced to explain the mechanism of seizures in essential epilepsy, the most nearly satisfactory one, in our opinion, is that which relates it to disturbances in certain physicochemical processes, such as those involved in the respiratory function of the brain cells or in the regulation of water and acid-base balance in the tissues. The important contributions bearing on the various angles of this new point of view have been admirably discussed by Lennox and Cobb [1] in their recent critical review of the literature on epilepsy and so need not take extra space here.

The present communication deals with but one phase of the subject, namely, that concerned with the acid-base equilibrium. The data presented have been obtained from cases in which a study of the blood lipides was simultaneously being made with the collaboration of Dr. W. R. Bloor.

Although a number of workers in Europe and in this country have interested themselves in the problem, there is as yet no concordance of opinion regarding the relationship of epileptic manifestations to the acid-base metabolism. Differences in the type of patient studied, in the patient's condition at the time of observation, in methods employed and in the interpretation of results obtained probably account for the marked divergence of opinions expressed. The first real intimation of a disturbance in the acid-base relationships in this disease appears to have come from the work of Bisgaard, Jarløv and Nørvig,[2] who found much greater irregularity in the relationship between ammonia nitrogen, total nitrogen and p_H of the urine in epileptic patients than that reported by

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* From the Department of Pediatrics, the University of Rochester and the Pediatric Service of the Strong Memorial Hospital.

* Read at the Annual Meeting of the American Society for Experimental Pathology at Ann Arbor, Mich., April 13, 1928.

1. Lennox, G. W., and Cobb, Stanley: Epilepsy: From the Standpoint of Physiology and Treatment, Medicine **7**:105, 1928.

2. Bisgaard, A.; Jarløv, E., and Nørvig, J.: Undersøgelser over neutralitetsregulationen ved geniun Epilepsi, Hospitalstid. **61**:960, 1918.

Hasselbalch [3] in normal subjects. Since the time of the first publication, evidence has been presented both for and against their conclusion. The problem has recently been restudied from the same angle by Ericksen, Levinsen and Warburg [4] who came to the conclusion that the original claim cannot be supported. They found that this so-called "dysregulation" may occur under other conditions and is not always found in epilepsy.

Jarløv [5] was the first to report a tendency for the blood reaction to swing toward the alkaline side preceding convulsions, but he presented a limited amount of evidence to prove it. Geyelin, Bigwood and Wheatley [6] concluded from a larger number of determinations that the variations in blood p_H are much wider in epileptic than in normal subjects, although other constant tendencies for that group of patients were not found. Bigwood,[7] who extended the study still further by use of a colorimetric p_H method (Cullen [8]), found values similar to these, but in addition, a definite tendency for a state of alkalosis to precede attacks, as claimed by Jarløv. These abnormal observations were confined to cases of idiopathic epilepsy, patients with the typical jacksonian seizures showing no such variations. Various other workers [9] have been unable to agree entirely with these conclusions. Marrack and Thacker,[10] whose methods were carefully checked, found the same range of blood p_H values in eight cases of epilepsy that they found in normal controls. From a comprehensive review of the literature, Lennox and Cobb [1] concluded that an abnormality in the acid-base equilibrium has not been demonstrated, if 7.3 and 7.5 are accepted as the limits of normal blood p_H values. However, the main evidence, as they have pointed out, is in

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3. Hasselbalch, K. A.: Ammoniak als physiologischer neutralitatsregulator, Biochem. Ztschr. **74**:18, 1916.

4. Ericksen, K.; Levinsen, H., and Warburg, E.: Studies and Deliberations on the Acid-Base Metabolism of the Organism with a Special View to Disturbances of Same in Nervous Diseases, Acta med. Scandinav. **65**:209, 1927.

5. Jarløv, E.: Sur l'équilibre acido-basique du sang humain etudié dans ses rapports avec diverses affections, Compt. rend. Soc. de biol. **84**:156, 1921.

6. Geyelin, H. R.; Bigwood, E. J., and Wheatley, M. A.: The Reaction of the Blood in Epilepsy, Proc. Soc. Exper. Biol. & Med. **21**:227, 1923.

7. Bigwood, E. J.: Perturbation de l'équilibre acide-base du sang dans l'epilepsie, Compt. rend. Soc. de biol. **89**:839, 1923; L'équilibre physico-chemique du sang dans l'epilepsie, L'ion calcium, J. de physiol. et de path. gén. **22**:70, 1924.

8. Cullen, G. E.: Studies of Acidosis; Colorimetric Determination of Hydrogen Ion Concentration of Blood Plasma, J. Biol. Chem. **52**:501, 1922.

9. Frisch, F., and Fried, E.: Zur Frage der angeblichen Alkalose bei Epilepsie, Ztschr. f. d. ges. exper. Med. **49**:462, 1926. Dautrebande, L.: L'équilibre acide-base du sang dans l'épilepsie, Compt. rend. Soc. de biol. **94**:133, 1926. Marrack, J., and Thacker, G.: Reaction of Blood in Epilepsy, Brit. J. Exper. Path. **7**:265, 1926.

10. Marrack and Thacker (footnote 9, third reference).

favor of the claim that the degree of fluctuation within these limits is unusually great in epilepsy, with a definite tendency toward the higher values.

Lennox and Allen [11] found the plasma bicarbonate within the limits of from 55 to 70 per cent by volumes in all but 12 of 100 patients. The abnormalities found, however, occurred on the alkaline side. Our own figures, as well as those of Dautrebande [12] Frisch and Fried,[13] Mordre [14] and others, cover a similar range. The fixed bases of the blood have been reported to be normal by Hamilton [15] and by Blumgarten and Rohdenburg.[16] Gamble and Hamilton [17] did not discover any abnormalities in the acid-base composition of the urine of an epileptic child who was studied continuously over a period of four weeks during which she had several series of seizures at almost regular intervals. They did find, however, a marked increase in the excretion of total acid, total base and extracellular water during the short periods when she had seizures.

Indirect evidence in favor of the assumption of a disturbed acid-base balance in idiopathic epilepsy is found in the observation that the occurrence of seizures is favored by such diverse factors as overventilation of the lungs, ingestion of alkali and short periods of anoxemia,[1] which have in common the effect of making the blood more alkaline. Furthermore, procedures which tend to produce mild acidosis, such as fasting, the use of a ketogenic diet, administration of carbon dioxide, or the ingestion of large doses of acid-forming salts [1] tend also to prevent or to alleviate the manifestations of the disease. We have found that the effectiveness of the ketogenic diet in preventing seizures is abolished, if it is made to have a slightly alkaline instead of an acid ash.[18]

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11. Lennox, W. G., and Allen, M.: Studies of the Metabolism in Epilepsy: IV. The Plasma Bicarbonate, Arch. Neurol. & Psychiat. (in press), quoted by Lennox and Cobb (1).

12. Dautreband (footnote 9, second reference).

13. Frisch and Fried (footnote 9, first reference).

14. Mordre, S. K.: Litt om alkalireservens forhold: organismen: nogen tilfaelder au epilepsi, Norsk. Mag. f. Laegevidensk. **83**:602, 1922.

15. Hamilton, B.: Comparison of Concentrations of Inorganic Substances in Serum and Spinal Fluid, J. Biol. Chem. **65**:101, 1925.

16. Blumgarten, A. S., and Rohdenburg, G. L.: Mineral Salt Content of the Blood in Disease, Arch. Int. Med. **39**:372 (March) 1927.

17. Gamble, J. L., and Hamilton, B.: The Acid-Base Composition of Urine from an Epileptic Child, Bull. Johns Hopkins Hosp. **61**:389, 1927.

18. McQuarrie, Irvine, and Keith, H. M.: Influence of Acid-Forming and Base-Forming Constituents of Ketogenic Diet Used in Treatment of Idiopathic Epilepsy, Proc. Soc. Exper. Biol. & Med. **25**:418, 1928.

PLAN OF STUDY AND METHODS USED

We are convinced that the most satisfactory method for determining the relationship of any particular change to the occurrence of seizures in epilepsy is that of studying the factors involved under controlled conditions, in which the various phases or cycles characterizing the disorder are represented. For the present study, therefore, patients were selected in whom the response to fasting or the ketogenic diet was known. The plan followed was that of obtaining data during periods of freedom from seizures, that is, while the patient was on the ketogenic regimen, and again at intervals after the institution of various procedures calculated to cause their recurrence. In one experiment, lasting over a period of forty-one days, dietary changes alone were involved. In the more acute experiments, recurrences of attacks were brought about by the administration of alkali, carbohydrate or carbohydrate and insulin to subjects with well established dietary ketosis. In two mild cases, attempts were made to induce seizures during the comparatively long free intervals between regular attacks by the administration of alkali. Full cooperation of the patients and their parents was secured in all cases.

The carbon dioxide content of the plasma was determined by the method of van Slyke,[19] on blood samples taken over mercury. For the total acetone bodies of the blood and the urine, the colorimetric method of Behre and Benedict [20] was used. The total titratable acid of the urine was measured by the procedure of Henderson and Palmer.[21] For determining the blood p_H we have used a special colorimetric method [22] based on the plasma dilution principle of Cullen,[8] but in which color comparisons are made at 38 C. with the bicolor standards of Hastings and Sendroy.[23] The advantage of this method is that the blood is taken over mercury directly into a special sampling tube containing previously adjusted indicator-saline solution, thus making unnecessary the transfer of the blood and the use of an anticoagulant and the protective layer of mineral oil required in other methods. After centrifugalization, the sample is placed in a water-bath at 38.5 C. for ten minutes and is then

19. Van Slyke, D. D.: Studies of Acidosis: II. A Method for the Determination of Carbon Dioxide and Carbonates in Solution, J. Biol. Chem. **30**:347, 1917.

20. Behre, J. A., and Benedict, S. R.: A Colorimetric Method for the Determination of Acetone Bodies in Blood and Urine, J. Biol. Chem. **70**:487, 1926.

21. Henderson, L. J., and Palmer, W. W.: On the Several Factors of Acid Excretion, J. Biol. Chem. **17**:305, 1914.

22. McQuarrie, Irvine: Determination of Blood p_H Without Transferring Sample, Proc. Soc. Exper. Biol. & Med. **25**:134, 1927.

23. Hastings, A. B., and Sendroy, Julius: Studies of Acidosis: XX. The Colorimetric Determination of Blood p_H at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**:695, 1924.

read in a comparator block against standards kept in tubes with the same diameter as the sampling tube. For human blood, we have not found it essential to carry out the procedure of Austin, Stadie and Robinson,[24] their "H" correction being unnecessary under these circumstances. We believe that the relative degree of accuracy possible by the procedure used gives significance to p_H values ranging outside the limits of 7.33 to 7.41, which mark the zone of normal variations in children, at least during the postabsorptive period.

RESULTS OF EXPERIMENTS

The results recorded here are representative of a larger number of studies carried out along this line. A few of the first acute experiments have been omitted, however, because the data were incomplete. Those recorded serve to bring out the main facts observed. The order of presentation is approximately that in which the experiments were done.

The Effects of Various Dietary Regimens on the Occurrence of Seizures and on the p_H of the Blood.—The relative effectiveness of certain modifications of the dietary regimen in preventing seizures is brought out in chart 1. The subject of this experiment (M. P.) was an Italian girl, aged 13, weighing 36.6 Kg., who had had an essential epilepsy of a severe grade, for five years and frequent grand mal attacks, averaging under ordinary conditions from one to fifteen daily during the past year on an ordinary diet without medication. Her response to the ketogenic dietary regimen has repeatedly been proved by us to be prompt and comparatively complete. During the forty-one days of the experiment she was put on a fast four days at the beginning and four days at the end. Following the first fast, for a period of twelve days she was placed on a diet containing 36 Gm. of protein (1 Gm. per kilogram of body weight), 175 Gm. of fat and 9 Gm. of carbohydrate, the latter being selected largely from the list of acid-forming plant foods.[25] During the third period of six days, the same amounts of protein, fat and carbohydrate were given, but the carbohydrate was furnished in the form of strongly base-forming, low-carbohydrate vegetables in order to test the effects of an alkaline ash. Because of the low carbohydrate allowance, it was necessary to supplement the base derived from the diet with a small quantity of sodium bicarbonate. The amount added (1 Gm. with each meal) was determined from calculations of the base that might occur naturally in the

24. Austin, J. H.; Stadie, W. C., and Robinson, H. W.: The Relation Between Colorimetric Reading and True p_H of Serum or Plasma, J. Biol. Chem. **66**:505, 1925.

25. Sherman, H. C., and Gettler, A. O.: The Balance of Acid-Forming and Base-Forming Elements in Foods, and Its Relation to Ammonia Metabolism, J. Biol. Chem. **11**:169, 1912.

less strongly ketogenic diets given to our patients with mild forms of epilepsy. During the five days of the fourth period, a carbohydrate-free diet, consisting of 55 Gm. of protein and 110 Gm. of fat, was given. This was approximately equal to the preceding diets, as regards its caloric value and its fatty-acid to dextrose ratio. Following this, she was placed for ten days on a nonketogenic, carbohydrate-free diet, containing 200 Gm. of protein (5.5 Gm. per kilogram of body weight) and 110 Gm. of fat per day. The chief purpose of this diet was to ascertain how much effect the inorganic acid derivable from protein alone might have on the occurrence of seizures and on the acid-base equilibrium.

The most striking feaure of the data charted in this experiment is the variation in the number of seizures occurring during the different periods. It is obvious that the dietary regimens of the third and fifth periods were without effect in preventing attacks. It was somewhat surprising to find that the diet of period V, calculated to furnish an excess of inorganic acid equivalent to 1,110 cc. of tenth normal solution from its acid-forming elements, had no effect whatsoever in the direction of preventing seizures. The twenty-four hour output of urinary nitrogen during this period indicates that about five sixths of the quantity of protein in the diet was catabolized. If any change from the ordinary course for this patient followed the use of the diet, it was in the direction of increasing frequency of seizures. The three seizures recorded for period II occurred on two days, when the degree of ketosis had been markedly reduced by the inadvertent giving of extra carbohydrate with the diet. The fact that the few convulsions which occurred during period IV and the two fasting periods were in each instance on the first day only indicates an overlapping of effects from the preceding regimens. Similarly, the beneficial effects of the ketogenic diets with acid residues are seen to be carried over into periods III and V. There is shown to be an inverse relationship between the degree of ketosis and the number of seizures throughout the entire experimental period, except for period III, in which the ketogenic diet was made to have a slightly basic ash. This is in agreement with our previous observations.[26] The relationship between the total titratable acidity of the urine and the frequency of convulsions was less well defined.

Figures for the p_H of the blood suggest a direct relationship to the frequency of convulsions, though the number of determinations made was limited. The two highest values recorded, namely, those on the fourteenth (7.53) and thirtieth (7.55) days, were obtained shortly after

26. McQuarrie, Irvine, and Keith, H. M.: Epilepsy in Children: Relationship of Variations in the Degree of Ketonuria to Occurrence of Convulsions in Epileptic Children on Ketogenic Diets, Am. J. Dis. Child. **34**:1013, 1927.

the midday meal. In each instance, it happened that the determination was made at about the midpoint between two grand mal attacks several hours apart. The values shown on the eighteenth (7.43), twentieth (7.50) and thirty-fifth (7.47) days were obtained one hour, one-half hour and ten minutes, respectively, before grand mal seizures. The low figure (7.25) obtained on the nineteenth day was for blood taken during a convulsion. The remaining fourteen determinations were made

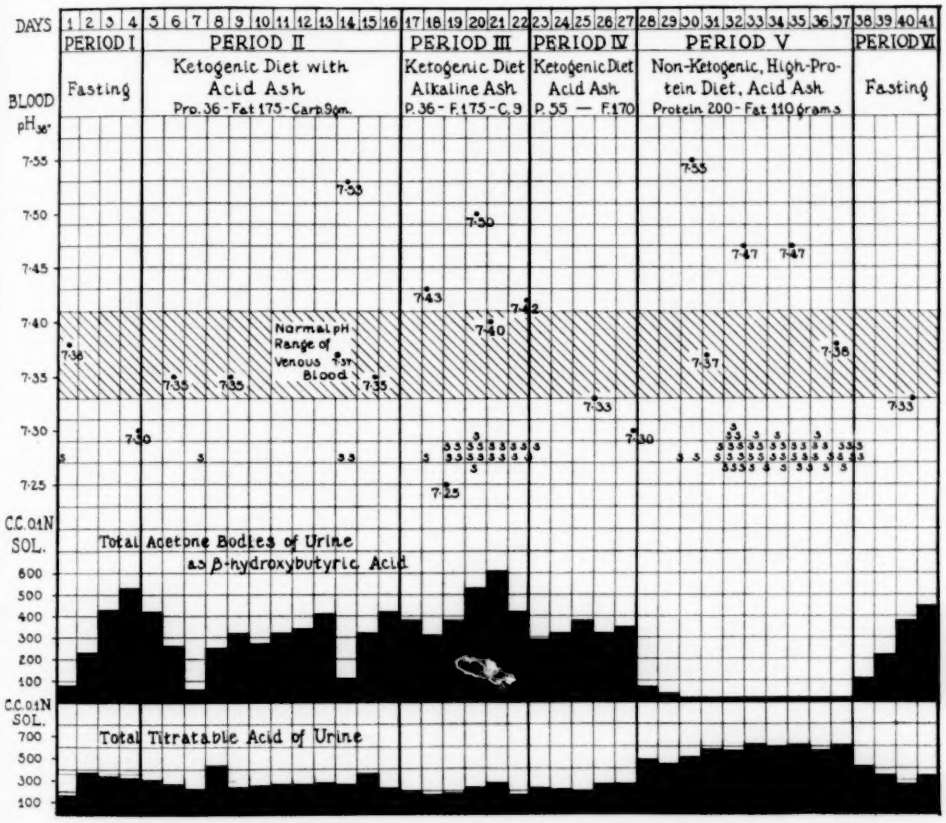

Chart 1.—Influence of various dietary regimens on occurrence of seizures in M. P. in relation to the total titratable acid and the acetone bodies of the urine and the p_H of the blood. *"S"* indicates the seizure.

at times more remote from seizures. The plasma carbon dioxide content, which was measured at the same time, followed the p_H closely in all except the one instance in which the blood was taken during a severe seizure. Accumulation of carbon dioxide at this time was of course a result of the convulsion itself.

Acute Experiments on the Relation of Acid-Base Equilibrium to Occurrence of Seizures.—In the following charts, data are presented

from a number of acute experiments planned with the hope of securing more definite information in regard to the relationship of changes in the acid-base balance to occurrence of convulsions. The concentration of blood acetone bodies was determined along with the p_H and the plasma carbon dioxide content in order to ascertain whether these have any specific inhibitory influence on the seizures apart from their acid effect.

Chart 2 shows the results of an experiment in which the beneficial effect of a strongly ketogenic diet was abolished within a few hours by the subcutaneous injection of one dose of insulin and the administration of large amounts of carbohydrate by mouth. The subject of this study

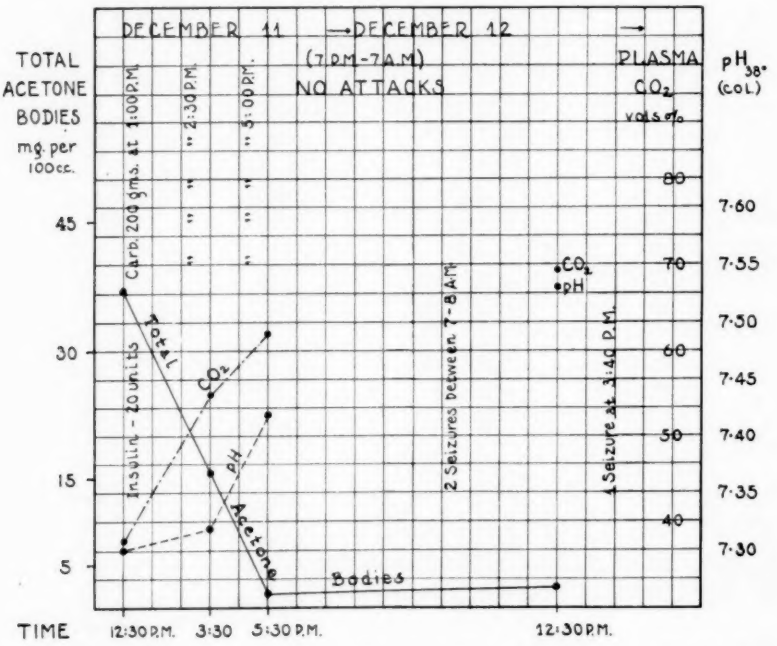

Chart 2.—Effect of relatively sudden removal of dietary ketosis by insulin and dextrose on recurrence of seizures in relation to change in the acid-base equilibrium of the blood in the patient, M. Y.

(M. Y.) was a fairly intelligent girl, aged 14, weighing 42 Kg., who was known to have at least a few petit mal seizures daily and occasional grand mal attacks as well. Prior to receiving the carbohydrate and insulin, she had been entirely free from seizures for eight days while on a strongly ketogenic diet consisting of protein, 42 Gm.; carbohydrate, 10 Gm., and fat, 200 Gm. Previously, she had been having from two to four seizures daily on an ordinary diet. The relatively high concentration of acetone bodies in the blood indicates the existence of a fairly marked degree of ketosis, which resulted in a definite though mild

acidosis. It can be seen from the chart that the carbon dioxide and p_H of the blood rose promptly with the reduction of the blood ketones to the normal level. It is apparent that a state of true uncompensated alkalosis developed after this point had been reached. So far as could be ascertained, seizures did not recur until fourteen hours later. The possible reason for this delay and that seen in the other acute experiments is discussed later. Unfortunately, the blood p_H and carbon dioxide were not determined immediately before these seizures. However, the fact that the p_H was 7.53 and the carbon dioxide 69 per cent by volumes five hours afterward and three hours preceding the next

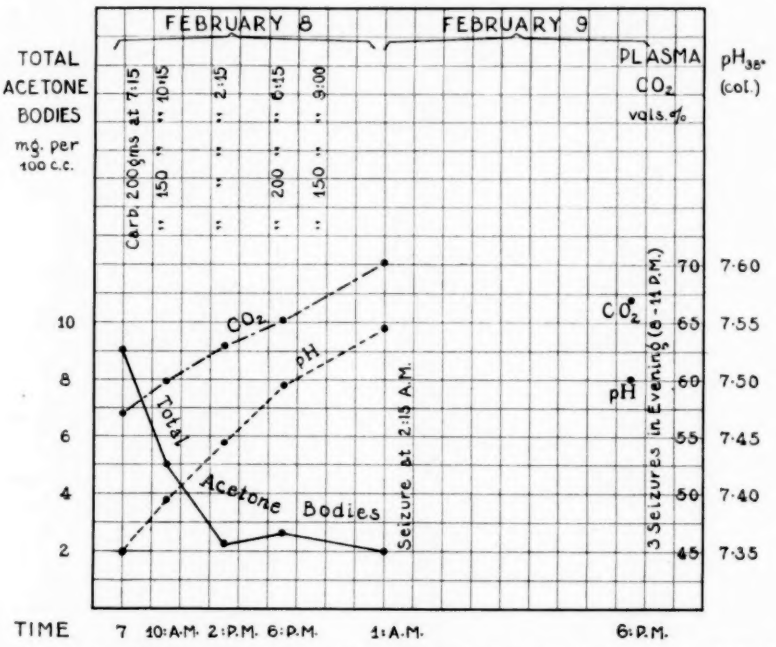

Chart 3.—Effect of relatively sudden removal of dietary ketosis by carbohydrate feeding on recurrence of seizures in relation to change in the acid-base equilibrium of the blood in the patient, M. P.

seizure is indicative of the existence of alkalosis at the time the seizures began.

The experiment shown in chart 3 is similar to that just described except that the initial ketosis was less intense; the carbohydrate alone was given to reduce it, and the blood sample was obtained nearer the time of the first seizure. The subject of this experiment, M. P., aged 13, and weighing 36.6 Kg., was also the subject of the long study described in chart 1. At the time of the present experiment she had been free from seizures but thirty-six hours on the ketogenic regimen containing:

protein, 36 Gm.; carbohydrate, 9 Gm., and fat, 175 Gm.; this followed a period when she had been out of control and having from two to fifteen seizures daily on a more liberal diet. It is seen again here that seizures did not recur for a number of hours after the blood ketones had returned to normal and that the carbon dioxide and p_H had risen to a level indicating mild alkalosis. Values for the latter were still elevated in the evening of the same day, two hours before a second recurrence of seizures.

A different type of experiment is illustrated in chart 4. In this instance alkalosis was produced in a severely epileptic child during a

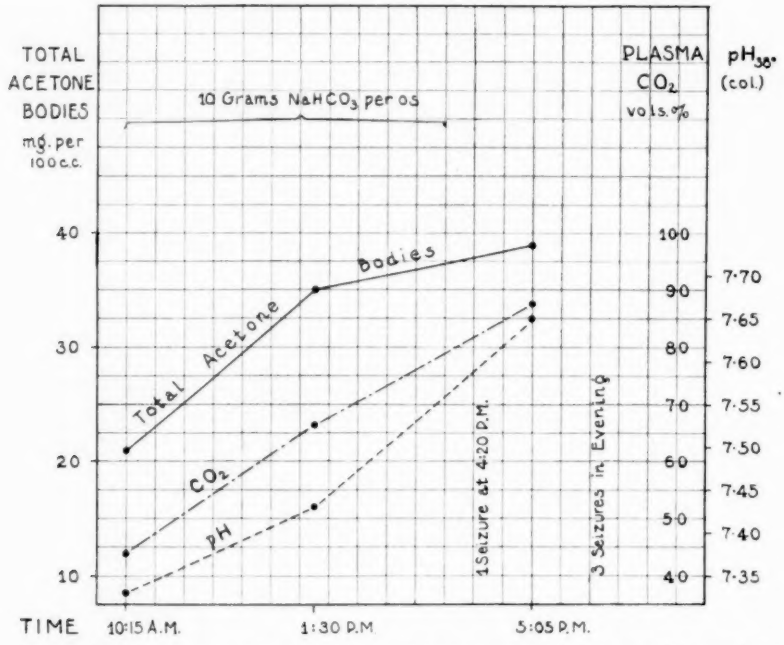

Chart 4.—Recurrence of seizures in relation to changes in the acid-base balance and the acetone bodies of the blood, following the ingestion of sodium bicarbonate by patient, S. G.

period of intense dietary ketosis by the administration of sodium bicarbonate. The subject (S. G.) was a boy, aged 5, weighing 14 Kg. For nearly a year he had been having grand mal and petit mal seizures with increasing frequency. Before admission for the present study, he had been averaging from two to five attacks daily, the majority occurring at night. His clinical response to the ketogenic diet, which contained 21 Gm. of protein, 5 Gm. of carbohydrate and 10 Gm. of fat, was less favorable than that of many other patients. Prior to the time

of this experiment, he had been entirely free from convulsions for three days, although previous to that he had had four to seven seizures daily on an ordinary diet.

Seizures recurred within six hours after the intial dose of alkali was given. The patient complained of a more or less typical aura following the third dose of alkali, but failed to have a seizure until after the fifth dose was given four hours later. Preceding the latter, he had a definite aura similar to the first. While the blood was not sampled for its carbon dioxide and p_H values immediately before the attack, it is certain that these contents were rising rapidly at the time and must have

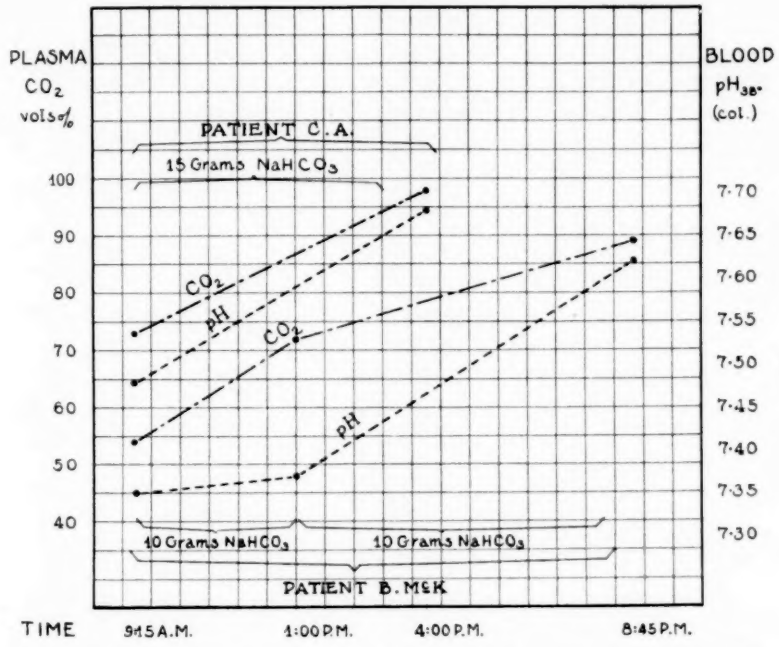

Chart 5.—Unsuccessful attempts to induce seizures during free intervals by the production of marked alkalosis in patients, C. A. and B. McK.

been well above the normal range as indicated by figures obtained forty-five minutes later. The recurrence of three severe seizures between two and three hours after this determination is confirmatory evidence. We have repeatedly observed similar results from the administration of alkali to patients with a severe form of epilepsy who were made temporarily free from seizures by fasting or the ketogenic diet.

That the concentration of acetone bodies in the blood bears little relationship to the prevention of seizures apart from their acid effect is shown in this experiment. It is evident that the same agent in this

instance produces both an increase in the total acetone bodies of the blood and a recurrence of seizures.

In order to determine whether the epileptic subject always responds to alkalosis by having seizures, the three following experiments were carried out. In the first two of these (chart 5) two patients known to have typical epileptic convulsions at more or less regular periods were given sufficiently large doses of sodium bicarbonate during the intervals between attacks to produce marked alkalosis, as shown by the plasma carbon dioxide and p_H values. In the case of C. A., a girl, aged 12, weighing 33 Kg., there had been a series of grand mal seizures at

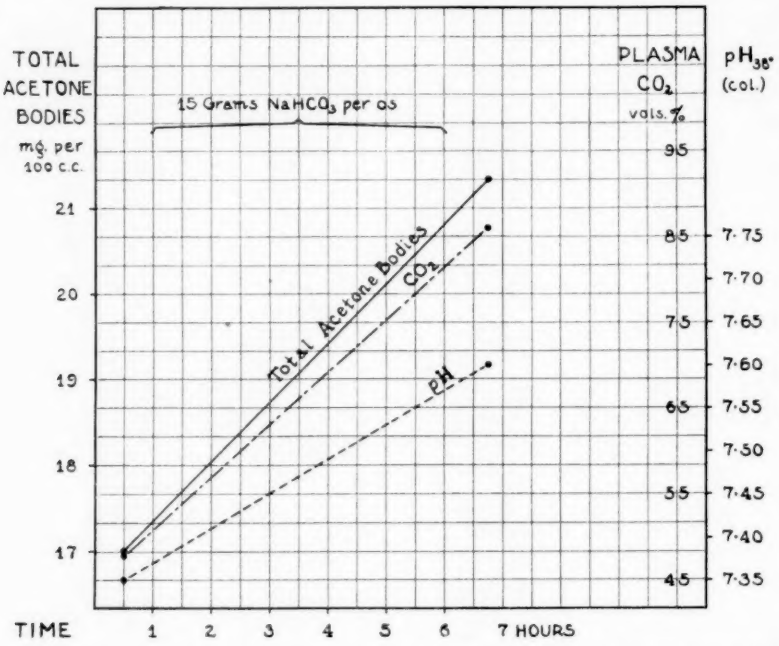

Chart 6.—Unsuccessful attempts to induce seizures during free interval by the production of fairly marked alkalosis in the presense of ketosis in patient, B. McK.

intervals of from three to seven weeks for three years; however, seizures had not occurred for two weeks on an ordinary diet. A state of alkalosis was maintained over a two-day period, the carbon dioxide and p_H values shown on the chart being those from the second day only. The second subject (B. McK.), a girl, aged 10, weighing 30 Kg., had been having grand mal seizures, increasing in frequency during the past two years. The attacks were occurring at weekly or biweekly intervals at the time of the experiment. The last seizure had occurred one week previously on an ordinary diet. She was given the alkali but one day. In spite of the marked alkalosis

produced, both patients remained free from attacks. Neither had a symptom that could have been interpreted as an aura during this period, even when the effect of overventilation of the lungs was superimposed on that of administration of the alkali. This patient was later found to respond well to a ketogenic diet.

The results from the third number of this series of experiments are presented in chart 6. The subject of this study was B. McK., mentioned in the preceding paragraph. The diet in this case consisted of protein, 30 Gm.; carbohydrate, 8 Gm.; fat, 125 Gm. This experiment differed from the two preceding ones in that the patient was allowed to develop a marked grade of dietary ketosis before alkali was given, in order to ascertain whether a sudden shift from a state of mild acidosis to one of alkalosis might be more effective in inducing seizures. The results, however, were the same; namely, the production of a fairly intense grade of alkalosis without the slightest evidence of a seizure or other manifestation of active epilepsy. Repeated attempts to cause a recurrence of seizures during the free periods by administration of carbohydrates in large amounts have likewise failed. Both of the patients taking part in these three experiments have since had typical convulsions, but they did not occur for several weeks after discharge from the hospital.

COMMENT

On the whole, the data presented here lend support to the claim for a disturbance of acid-base equilibrium in essential epilepsy; however, they do not indicate by any means that this is the only factor or even the main one involved. On the contrary, it seems probable to us that this abnormality is merely incidental to a more basic disturbance in the metabolism of brain cells or in the physicochemical processes concerned with the functions of the surface membranes of the cells.

Be this as it may, it is apparent from chart 1 that the patient with severe epilepsy of the type under discussion responds differently to the various dietary regimens used. It is evident that fasting and the ketogenic diets with a preponderantly acid ash both tended to prevent seizures to a striking degree, whereas, the ketogenic diet with a slightly alkaline ash and the nonketogenic diet with a highly acid ash did not have any inhibiting effect. No matter how this observation may be interpreted, a fairly striking feature of the experiment was the observation of normal or slightly lower p_H values of the blood during periods of freedom from seizures and a tendency for higher values, when seizures were frequent. The increased p_H values obtained just before or a few hours after convulsions under the controlled conditions of this experiment confirm the reports of Jarløv and of Bigwood. We have found results similar to these in a few other patients of the same type (known

to respond favorably to fasting or the ketogenic diet), when we have been fortunate enough to obtain blood samples shortly before seizures. However, in the case of one patient, clinically of the same general type but responding unsatisfactorily to the diet, p_H values of the blood (7.4 and 7.38) within the upper limits of normal were obtained immediately before seizures on two occasions.

This experience has led us to wonder if there might not be different etiologic factors in different subgroups of the large heterogenous class of "essential" or "idiopathic" epileptic persons. This admittedly scanty evidence, together with the conflicting reports in the literature, suggests the possibility of there being one subgroup of cases in which a disturbance in the acid-base equilibrium occurs and another in which it does not occur. If such were found to be the case, the former group would probably be identified as that which responds to measures preventing shifts in the acid-base balance toward the alkaline side; the latter would include those that do not so respond. As yet, on observation from time to time of the type of response to the ketogenic regimen we have not noted sufficiently great variation on the part of any patient to account for this difference.

The results of the acute experiments presented in charts 2, 3 and 4 likewise tend to support the thesis that mild alkalosis is present before seizures occur. Whether the extent of the shift in the reaction of the blood toward the alkaline side was greater in these epileptic subjects, following the sudden reduction of ketosis by the different procedures, than it would be in normal subjects under identical conditions is a crucial question which cannot be answered from the data available at present. The delay in the occurrence of seizures after the development of alkalosis in these and other similar experiments has interested us. The true explanation of this delay would doubtless contribute materially to an understanding of the mechanism of the seizures.

One suggestion is found in somewhat analogous experiments on the dog by Gesell and Hertzman [27] in their studies on the regulation of respiration. They found that the tissues, cerebrospinal fluid and blood became more acid immediately following administration of carbon dioxide; whereas, they promptly became more alkaline following the intravenous injection of sodium carbonate. Sodium bicarbonate was found to have an intermediate effect, causing an increase in the alkalinity of both the arterial and venous blood but a temporary increase in the acidity of the tissues and the cerebrospinal fluid. They interpreted these observations as suggesting a difference in permeability of cell membranes to the various ions of the bicarbonate buffer system. Following the

27. Gesell, R., and Hertzman, A. B.: The Regulation of Respiration: Tissue Acidity, Blood Acidity and Pulmonary Ventilation, Am. J. Physiol. **78**:610, 1926.

initial downward swing in the p_H of the cerebrospinal fluid, which remained on the acid side for a considerable period of time, they usually found a definite shift to the alkaline side near the end of their experiments. This final change was attributed in part to the tissue abuse incident to periods of deprivation of oxygen in the experiment. Following the injury produced by low oxygen tension or injection of sodium cyanide, it was observed that the cerebrospinal fluid became alkaline almost as quickly as the blood after administration of sodium bicarbonate. It seems plausible that the delay in occurrence of seizures in our experiments especially after administration of sodium bicarbonate is dependent on a similar behavior of the membranes in the central nervous system toward the basic ions, several hours being required for equilibrium to be established on the higher p_H level. For the purpose of testing this possibility, data are now being obtained on the spinal fluid as well as on the blood. A possible explanation for the greater resistance of the normal subject (or of the epileptic subject during free intervals) to procedures producing excessive alkalinity of the blood may be that the membranes of the nerve cell involved remain impermeable to the added basic ions for a sufficiently long period to allow their excretion by the kidneys.

Whatever the underlying disturbance in epilepsy may be, it is apparently operative during what may be called the "active phase" only. So far as our "provocative" tests can be relied on as criteria, the subject with less severe epilepsy is not different from the normal person during the long intervals between attacks. Such an observation is encouraging, because it emphasizes the probability that this type of epilepsy has a functional rather than a purely structural basis. What is of still further interest, is the fact that the course of the disease can be influenced at least temporarily by such simple procedures as changes in the dietary regimen.

A satisfactory explanation, regarding the cause of the slight alkaline shift in blood reaction observed in some cases before seizures, would probably go a long way toward an understanding of the etiology of this baffling clinical syndrome. At present the mechanism is entirely obscure. The fact that overventilation of the lungs will frequently bring on seizures, suggests the possibility of oversensitiveness of the respiratory center, but the observation of normal or increased blood carbon dioxide immediately before attacks tends to rule this out. Failure in the excretion of base by the kidneys or excessive loss of acid by way of the urine or in the alimentary tract are unlikely in light of the study by Gamble and Hamilton [17] already referred to. Disease of the parathyroid gland in epilepsy has not been shown to exist, nor does there seem to be any convincing evidence of increased blood ammonia, or abnormality in the urinary ammonia accompanying the convulsive state. One of the

striking results of fasting, as shown by the extensive study of Gamble, Ross and Tisdall,[28] is the loss of intracellular water and fixed base, incident to the excretion of the excessive amounts of acid formed. The strongly ketogenic diet with a relatively low protein content appears to have a similar effect. The efficiency of these two measures in preventing seizures, therefore, suggests again that the seat of the difficulty may be in the brain cells themselves. The nature of this assumed underlying abnormality in the physiology of these cells or of their membranes is entirely obscure. The possibility of its being dependent on a disturbance in the lipid metabolism seems promising to us. In collaboration with Dr. W. R. Bloor a study in that comparatively difficult field was begun nearly two years ago. Any detailed discussion at this time of the results obtained would be premature, but it can be said that they are encouraging.

SUMMARY AND CONCLUSIONS

The acid-base equilibrium has been studied in children with essential epilepsy under fairly well controlled conditions. The general plan of study was that of placing patients with severe epilepsy on the ketogenic dietary regimen until they were definitely prevented from having seizures and then modifying conditions in various ways to cause recurrence of attacks. The carbon dioxide content of the blood plasma and the p_H and total acetone bodies of the whole blood were determined at intervals before and after such changes. In two cases of epilepsy, in which infrequent attacks occurred, attempts to induce seizures during the free intervals by the production of severe alkalosis were made.

Administration of carbohydrate to one patient with severe epilepsy and carbohydrate and insulin to another, while they were under dietary control, caused recurrences of seizures within nineteen hours. The seizures did not occur until approximately twelve hours after the acetone bodies of the blood had been reduced to the normal level and after the p_H and carbon dioxide values indicated the presence of a mild degree of alkalosis. In another case recurrence of seizures followed within a few hours after a mild dietary acidosis had been suddenly replaced by an uncompensated alkalosis resulting from the administration of sodium bicarbonate. The marked increase in concentration of the acetone bodies following the ingestion of bicarbonate indicates that these substances have little or no inhibitory effect on the convulsions in the presence of alkalosis. A possible reason for the delay in occurrence of seizures after the establishment of an abnormal degree of blood alkalinity in these acute experiments is considered. Attempts to induce seizures in mildly

28. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: The Metabolism of Fixed Base During Fasting, J. Biol. Chem. **57**:633, 1923.

epileptic subjects during the free intervals between their attacks by the production of marked alkalosis were unsuccessful. The possible significance of this result is discussed.

One patient with severe epilepsy was observed over a period of forty-one days in order to compare the effects (1) of fasting, (2) of a ketogenic diet with a predominantly acid ash, (3) of a ketogenic diet with an alkaline ash and (4) of a nonketogenic, high-protein diet with a strongly acid ash, on the occurrence of convulsions. The periods showing the fewest convulsions were those in which the patient fasted or was on a ketogenic diet having an acid ash. The effectiveness of the ketogenic diet was abolished, when it was made to have a slightly alkaline ash. With the exception of this alkaline-ash period, there was throughout an inverse relationship between the amount of acetone bodies excreted and the number of seizures occurring. The nonketogenic diet with an exceedingly high content of acid-forming elements did not have any inhibitory influence whatsoever on the convulsions. Careful measurements of the p_H of the venous blood at intervals throughout the course of this experiment indicate a tendency for the blood reaction to shift beyond the alkaline side of the normal range during periods of frequent seizures but to remain within or below normal range at other times. In a few instances it was found to be above the normal level immediately preceding or an hour or two after severe seizures.

The opinion is expressed that the abnormality in acid-base balance observed in certain cases of epilepsy is probably not the factor of chief importance in the mechanism of seizures, but is an incidental accompaniment of a more basic disturbance in the physiology of the nerve cell.

WHEAL FORMATION IN INFANTS AND IN CHILDREN

III. IN DEHYDRATION *

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In a previous publication,[1] facts were presented showing that an adequate circulation was necessary for the production of wheals in the human skin, and certain clinical conditions were discussed in which lessened or absent wheal formation following the intracutaneous injection of a codeine solution was attributed to decreased circulation in the skin. In this group were a limited number of patients who were acutely dehydrated, but the data were insufficient to decide whether actual decrease in blood volume, because of the dehydration, was the fundamental factor in the lessened circulation on which decreased wheal formation depended. It seemed worth while, therefore, to continue these observations to learn whether dehydration itself, independent of other factors, such as low blood pressure, would decrease the peripheral blood flow sufficiently to lessen wheal formation. The reaction to the intracutaneous injection of codeine was taken as a representative of the class of substances that produce wheals.

Accordingly, with this object in view, wheal formation in a considerable number of infants suffering from dehydration has been studied. Dehydration was seldom met as a primary condition, but was usually secondary to nutritional disturbances or infections or both, so that these other factors must be considered; however, an occasional subject was considered to be dehydrated primarily, that is, from the insufficient intake of fluid as a result of lack of care. Various types or stages of dehydration were studied, viz., acute and chronic, mild and severe. The majority of the subjects, especially those in the acute stages, were dehydrated on admission to the hospital; others became so during the period of hospitalization, in such conditions as the advanced stages of tuberculosis and other infections.

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* Submitted for publication, Aug. 3, 1928.

* From the Babies' and Children's Hospital and the Department of Pediatrics, Western Reserve University.

1. Pilcher, J. D.: Wheal Formation in Infants and in Children: I. In Edema, Cretinism, Scleredema, Sclerema, Nephritis, Cardiac Disease, Severe Prostration and Tuberculin Positive Subjects, Am. J. Dis. Child. **31**:77 (Jan.) 1926.

METHOD

Wheals were made by the injection of 0.1 cc. of 1:1,000 codeine phosphate in physiologic solution of sodium chloride into the skin of the forearms toward the elbow. In a normal infant, the resulting wheal reaches the maximum of from about 1.1 to 1.3 cm. in diameter, occasionally being considerably larger, in from five to ten minutes and gradually disappears during the course of about an hour. In older subjects, the wheal is larger. The degree of local reaction is measured by the diameter of the wheal and the amount of induration of the surrounding tissues and the time of disappearance, the latter being roughly directly proportional to the size of the wheal. The injection of 0.1 cc. of the solution intracutaneously raises a wheal of from 0.6 to 0.7 cm. in diameter. A reaction was considered to be negative unless the resulting wheal became larger than the wheal produced by the injection. When possible, the wheal reaction was measured on different occasions as the subject's condition changed, either improved or became worse; thus the reactions in a number of infants and children were followed until the subjects became normal or until their death.

The character of the wheal in the severely dehydrated subject differs materially from that formed in the well nourished person, in whom the injection of codeine induces much induration of the subcutaneous tissue. In the dehydrated subject, the reactive area is limited largely to the skin itself, because of the lack of subcutaneous tissue, so that the site of the wheal can be readily picked up and rolled between the finger and thumb, as can be done with the skin in the areas not receiving injections. This is not possible in the well nourished subject because of the induration of the subcutaneous tissue. Occasionally the wheal is broad but does not have any thickness, resembling a plaque. In the dehydrated subject, too, the vascular flush about the wheal is either decreased or absent, roughly proportional to the size of the wheal. Because of the difficulty in measuring the size of the wheal and the extent of the flush in these subjects, it could not be determined readily whether or not the decrease in flush preceded the decrease in the size of the wheal. Many of the most decisive results were in negro subjects, in whom it is usually impossible to determine the extent of the flush.

THE RESULTS IN SEVERELY DEHYDRATED SUBJECTS

In such subjects, especially if the dehydration was of rather sudden onset, an extremely small wheal was formed or none at all, the injected fluid being absorbed readily; this phenomenon occurred although the blood pressure was normal. It was observed that this result usually indicated that the infant's condition was low, and the prognosis was guarded, especially, in my experience, if the cause was an infectious diarrhea or a severe

nutritional disturbance associated with a primary infection outside the gastro-intestinal tract. Death has been the outcome in some of these patients without increase in the size of the wheal reaction. In the subjects who recovered, the area of the wheal reaction almost invariably returned to normal somewhat before the general normal condition of the patient, including the weight, was regained. This was usually the course when rapid progress was made, so that within a few days much of the

Examples of Wheal Formation in Subjects Dehydrated from Different Clinical Conditions

Case	Date	Age in Months	Weight Gm.	Wheal: Diameter in Cm. *	Wheal: Induration	Wheal: Disappearance Time in Minutes	Comment
113	5/19	5½	3,100	0.8 × 0.8	0	25	
	5/21	...	3,450	1.3 × 1.3	++	60	Acute dehydration with rapid recovery
	5/23	...	3,600	0.9 × 1.2	++	60	
	5/26	...	3,650	0.9 × 1.3	++	60	
130	9/19	7½	5,600	0.9 × 0.9	0	35	Decomposition; fairly rapid recovery; unusually large reaction
	9/26	...	5,900	1.0 × 1.3	+, ++	85	
	11/ 3	...	6,200	1.2 × 1.4	+++	90	
	12/ 8	...	7,000	1.3 × 1.7	+++	120	
169	9/29	10	4,700	0.7 × 0.8	0	20	Enteritis; improvement after infusions; death in eighteen hours
	9/30	...	4,925	1.0 × 1.2	+	60	
143	12/ 4	2	2,800	0.6 × 0.6 (neg.)	0	10	Severe dehydration from decomposition with diarrhea; slow recovery
	12/ 5	...	2,700	0.6 × 0.6	0	15	
	12/ 8	...	3,050	0.7 × 0.8	+	15	
	12/10	...	3,100	0.7 × 0.8	+	25	
	12/12	...	3,250	0.8 × 0.9	+	25	
	12/15	...	3,350	0.9 × 0.9	+	25	
	1 / 5	...	3,800	1.0 × 1.2	++	45	
	1 / 9	...	4,050	1.0 × 1.3	++	55	
135	10/ 2	5	5,400	1.0 × 1.1	++	60	Meningitis
	10/ 4	...	5,350	1.1 × 1.0	++	60	
	10/ 8	...	5,100	0.9 × 0.9	+	45	
	10/13	...	5,000	0.7 × 0.8	+	40	
	10/22	...	4,500	0.6 × 0.6 (neg.)	0, +	20	
	10/22	...	4,500	0.5 × 0.6 (neg.)	0	10	Death four hours later
100	7/30	36	.....	0.9 × 1.3	++	30	Pulmonary tuberculosis
	8/ 5	...	.....	0.9 × 1.0	+	25	
	8/ 8	...	.....	0.7 × 0.9	+	20	
	8/11	...	.....	0.6 × 0.7 (neg.)	0	0	

* The injection of the codeine solution intracutaneously raises a wheal from about 0.6 to 0.7 cm. in diameter, so that unless a wheal is somewhat larger than this the reaction should be considered as negative.

weight had been regained, or when the return to normal was a question of weeks. As an example of a prompt recovery, the following experience is presented: An emaciated negro infant, aged 5 months, who weighed 3,100 Gm., had a subnormal temperature and a scarcely palpable radial pulse on admission to the hospital. Under the application of external heat, the temperature soon became normal, the skin warm and the pulse readily palpable. Even at this stage practically no wheal followed the injection of codeine; with the use of infusions and the usual treatment of such patients, the improvement was rapid, and in three days the wheal reaction was about normal for infants of his age (113 in the

accompanying table). Such prompt recovery is exceptional, however. Rarely in severe dehydration, following the institution of saline infusions, has there been a temporary and considerable increase in the size of the wheal reaction, with a return to the previous condition in a few hours (169 in the table). In the severely dehydrated subjects, however, the usual course of events was the return of the general condition and the weight of the patient to normal, only after weeks had elapsed; concomitant with this gradual improvement, there was also a gradual increase in the degree of the wheal reaction, such as is shown in subject 143 in the table.

A considerably larger number of the infants examined entered the hospital in a state of chronic undernourishment, commonly less dehydrated than the members of the former group, but many of them emaciated and suffering from marked loss of tissue as well as loss of water. The latter group included infants in the various stages of decomposition or marasmus, with diarrhea of nutritional and infectious origin. The wheal reaction under such conditions was practically always below normal, but was surprisingly large in spite of the relatively poor condition of the subjects. For some time, the results were rather puzzling, until finally it was realized that in order to lessen wheal formation, other conditions being equal, a considerable degree of dehydration is necessary. From the data derived from a considerable number of cases the impression is that the acutely dehydrated subject reacts to a lesser degree by formation of wheals than does the more chronically dehydrated subject, the explanation probably being that the peripheral circulation in the subject in whom the loss of water has persisted for some time has remained more efficient than in those in whom the loss of water was acute, or that the circulation had become adjusted to the new conditions.

In older children, great loss of weight, whether directly due to dehydration or not, has a similar effect on wheal formation. A considerable number of children who had lost much weight in the course of infectious diseases, such as meningitis and chronic pulmonary infections and especially tuberculosis, were examined. In such subjects, much of the loss of weight was due to the actual loss of tissue as well as to the loss of water. When these children entered the hospital, the wheal reaction was about average for the weight and age, but with the increasing loss of weight the wheal reaction became smaller; usually a marked loss of weight was necessary, however, to lessen materially the size of the wheal. The reaction has been followed in a few subjects as the wheals became extremely small and again increased in size as the subject's condition and weight improved. In a number of patients with fatal tuberculosis, the wheal reaction and the reaction following the intracutaneous injection of tuberculin have been followed until the death of the patient; the degree of reaction of the two ran fairly parallel, i.e., as the disease

progressed and the subject lost weight, both reactions became less and finally failed entirely. (This refers to the 1 : 1,000 dilution of tuberculin and rarely to the 1 : 10 dilution also.) This was especially noted in the chronic forms of pulmonary tuberculosis (100 in the table) in which the wasting was severe and was due in part to the loss of tissue and in part in the late stages to low blood pressure, a factor to be discussed later. In acute forms of tuberculosis, in which death follows a fairly rapid course, viz., the acute miliary and meningeal forms, neither the wheal reaction nor the reaction following the injections of tuberculin are lost, although they may be lessened somewhat, because there is not sufficient dehydration, loss of tissue or low blood pressure to lessen the peripheral circulation to the degree necessary to prevent local vascular reactions. In well nourished persons, the reaction following the injection of codeine may fail shortly before death because of circulatory failure.

Blood Pressure Factor in Wheal Formation.—As has been stated, an adequate circulation is necessary for wheal formation. The blood flow is determined by several factors, among which are blood pressure, blood volume, viscosity and vascular tonus. As the blood pressure is usually fairly readily determined, records were made during the progress of the wheal test in a considerable number of subjects, and the following facts were learned: Wheal production may be greatly lessened, even almost abolished, with a normal systolic blood pressure for infants and young children, i. e., as high as from 104 to 112 mm. This was noted a number of times, but a single citation will suffice. A negro child, aged 3 years, suffering from advanced pulmonary tuberculosis, on three separate occasions when the systolic blood pressure was from 106 to 108 mm., gave a reaction of extremely small wheals, which were absorbed in about one-half the average time. Somewhat later, with a blood pressure of 86 mm., wheal formation did not follow the injection of codeine solution, at which level, as will be shown, normal wheals may form. Several small infants with a nutritional disturbance or infection gave extremely small reactions with a systolic blood pressure of from 106 to 112. At lower levels of blood pressure, the wheal reaction is usually much lessened; this was the result with pressures varying from 75 to 95 mm., although, even in considerably dehydrated subjects, the reaction was normal in a number of instances. Occasionally, too, in extremely small infants, when the blood pressure could not be determined and when the radial pulse was small, as as in one subject not palpable, wheals of average size and duration were formed; however, this result was unusual. These facts indicate that blood pressure of itself is only one factor in determining the peripheral blood flow.

COMMENT

The lessened degree of the local vascular reaction in the skin, as measured by the response to the intracutaneous injection of a codeine solution, in dehydrated subjects is considered to be due to the lessened circulation in the skin. The cause of the decreased peripheral blood flow was not investigated directly, as Utheim [2] has shown that in chronic nutritional disturbance there is a decreased peripheral circulation, as measured by Stewart's calorimetric method, the decreased flow depending in part on diminished blood volume and in part on peripheral vassoconstriction. A sufficient number of determinations were made to show that low blood pressure was not an essential factor in the lessened circulation, although it is a factor in some instances. The more marked decrease in wheal formation in the acutely dehydrated subjects, as compared with those in a state of chronic dehydration of a similar degree, indicates that the circulation in the latter is more efficient, without, however, explaining the mechanism of the adjustment.

CONCLUSION

In dehydrated subjects, there is a decreased wheal formation from the intracutaneous injection of a codeine solution, which is attributed to a lessened peripheral blood flow from a decreased blood volume.

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2. Utheim, K. A.: A Study of the Blood and Its Circulation in Normal Infants and Infants Suffering from Chronic Nutritional Disturbances, Am. J. Dis. Child. **20**:366 (Nov.) 1920.

EFFECT OF HIGH CEREAL DIETS ON THE GROWTH OF INFANTS*

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The importance of milk in a diet has been accepted so generally that scant attention has been given high cereal diets without milk, although the subject merits serious consideration, because rice eating races in the Orient not only have survived over a long period of time on this sort of diet, but have increased in numbers in spite of devastating epidemic diseases and an inadequate economic margin in years of flood and famine.

In China, one is struck by the fine physique, excellent teeth, strength and endurance of coolies, who have never tasted milk and who live on a diet in which rice furnishes a large proportion of the caloric intake. For example, in one day I have ridden as much as forty miles over country roads in China in a jinricksha drawn by a single coolie.

Cowgill and his associates[1] have made significant studies of the effect of abundant cereal intake in experiments on animals. They found that when suitable, adequate supplementary foods are employed, the use of whole grain cereals to furnish as much as 84 per cent of the calories of a diet is compatible with excellent growth, reproduction, lactation and general physiologic well-being in albino rats, and that the supplementary foods need not include milk.

The present study was undertaken to determine the effect of maternal diets, habitually high in cereal and lacking milk, on the growth and development of human infants. Clinical investigation is obviously not so exact and so well controlled as laboratory research, but the application of the results of experiments on animals to the human species has not been definitely determined; especially is this true when growth and development of the young are considered, because infancy and the period of growth are extremely brief in animals as compared with human beings.

MATERIAL

Ability to reproduce healthy offspring and to support good growth in infants during lactation are indications of the general excellence of a diet.

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* Submitted for publication, July 30, 1928.

1. Cowgill, G. R.: Jones, M. H.; Frist, R. A., and Jackson, G. P.: Studies on the Effects of Abundant Cereal Intake: I. The Use of Cereals as the Chief Source of Calories, J. A. M. A. **89**:1770 (Nov. 19) 1927; II. The Use of Supplements Other Than Milk, ibid. **89**:1930 (Dec. 3) 1927.

I examined 2,069 infants under 2 years of age, periodically, in health centers in the rural districts in Hawaii during the years 1926 and 1927, and kept records of the age, weight, gain in weight, dentition, skeletal development and other signs of normal development and good nutritional condition. Examinations were made as near as possible to the day of the month on which the child's birthday fell, so that the age groups might be as exact as possible.

There were 1,200 Japanese and 869 Filipino infants; 1,078 were males and 991 females. The diet of both the Japanese and the Filipino mothers contained abundant rice and no milk, but in other respects the Japanese diet was in general superior. In addition to rice, the Japanese eat generous amounts of vegetables, especially green vegetables, and small quantities of meat, fish and eggs. It is customary for both Japanese and Filipino mothers to suckle their young. Infants are nursed late and are rarely fed cow's milk. The infant mortality for the Japanese in Hawaii is far below the average for all races, while it is high for the Filipinos; so that these two races show the effects of a high cereal diet, with conditions favorable and unfavorable to infant life.

Hawaii is an excellent field for the study of race and the effect of racial diets, because it has a mild, favorable climate and is remarkably free from debilitating parasitic diseases which act as complicating environmental influences unfavorable to life. In an earlier paper,[2] it was pointed out that the growth of Chinese children of school age is considerably more rapid and regular in Hawaii than in China. Smellie and Augustine [3] reported that heavy infestations of hookworm cause marked retardation in normal growth in height and weight and lower the hemoglobin content of the blood in children of school age.

Reproduction.—The diet of the Japanese in Hawaii is adequate and suitable for the promotion of active reproduction because the birth rate is extremely high. According to the annual report of the President of the Board of Health of the Territory of Hawaii for the fiscal year ending June 30, 1927, the birth rate for the Japanese was 43.88; June 30, 1926, 43.37; June 30, 1925, 48.82, and June 1924, 47.33. Hawaii is in the death registration area of the United States but is not yet in the birth registration area, so if there is any error in these figures, the rates are probably too low. The Japanese population in Hawaii is established and relatively stable, because there is no immigration and little intermarriage with other races. The Filipino population, on the other

2. Appleton, V. B.: Growth of Chinese in Hawaii and in China, Am. J. Phys. Anthrop. **10**:237 (April-June) 1927.

3. Smellie, W. G., and Augustine, D. L.: Hookworm Infestation: The Effect of Varying Intensities on the Physical Condition of School Children, Am. J. Dis. Child. **31**:151 (Feb.) 1926.

hand, is changing rapidly, because immigration is in process, and the proportion of young adult males is relatively high but is not constant. The birth rates given for the Filipinos in the reports of the Board of Health are, therefore, dependent on too many undetermined factors to be of value for comparison.

Infant Mortality.—In the same annual reports of the President of the Board of Health, infant mortality rates are given as follows: 1924, all races 116.26, Japanese 87.46, Filipinos 262.55; 1925, all races 103.59, Japanese 59.81, Filipinos 287.38; 1926, all races 104.21, Japanese 72.76, Filipinos 237.19; 1927, all races 95.97, Japanese 55.65, Filipinos 226.25. As Hawaii is in the death registration area but not in the birth registration area, these rates may be slightly too high, but the error would probably be nearly the same for the Japanese and Filipino infants.

Weight.—Eight thousand two hundred and eighty-nine observations on the weight of infants, under 2 years of age, are included in the present study, 4,566 observations for Japanese and 3,723 for Filipino infants, 4,364 for males and 3,925 for females. The infants were weighed nude, and the weights were recorded in pounds and ounces. The weights that were not taken within three or four days of the date of a child's monthly birthday are excluded, except for the groups for infants aged 21 and 24 months, in which a little wider range is allowed. For example, the average weight at 2 months means two months by the calendar, plus or minus not more than three or four days, and does not mean the average of all infants whose age was between 1½ and 2½ months nor of those whose age was from 2 months up to just less than 3 months. All observations of weight which fall within this narrow age limit are included irrespective of the number of other age groups into which a given case may fall. It is not merely the average weight of a particular group that is of interest, but the range of weights for all infants who survive to attain a given age.

Gain in Weight.—The actual increase in weight was determined for the individual infants under observation. Four thousand four hundred and seventy observations on the gain in weight are considered, 2,492 for Japanese and 1,978 for Filipinos; 2,473 for males and 1,997 for females. Here again only those weights are included which fall within a few days of a given age. The gain in weight was often irregular. When an unusually big gain occurred one month, there might be little if any the following month. To offset these irregularities in the monthly increase in weight, the gain in weight is considered by the quarter and half year as well as by the month for the first twelve months of life.

Skeletal Development.—Infants were examined for craniotabes, rachitic beading of the ribs, Harrison's groove, flaring margin of the ribs, pigeon breast, broad epiphyses of the long bones especially at the

wrist and other abnormalities in the development of bones and the form of the chest. Bow legs were not considered, because the cramped position of the legs of Japanese babies when carried on their mothers' backs and the fact that both Japanese and Filipino infants are made to stand as early as at 2 or 3 months of age contribute mechanically to the development of bow legs. How far normal bones may deviate from normal form as a result of persistent faulty position and how much these variations are due to faulty calcification of the bone is a question.

An important additional factor is involved when the skeletal development is considered, because ultraviolet rays as well as diet have an important bearing on the calcification of bone. Hawaii is subtropical and has abundant sunshine, much reflected light from the sky and sea and days almost as long and as bright in winter as in summer. Furthermore, the mild climate permits outdoor life and extremely light clothing throughout the year. The infants examined always go barefooted and never wear hats. With few exceptions, they were deeply tanned over the face, neck, shoulders, arms, legs and feet. The exceptions were the children of shopkeepers who live in little shops which do not have a front wall during the day, so that the children get a great deal of reflected light and fresh air all day long but little direct sunshine.

Skin Color.—Tests were taken of the least exposed part of the body with the von Luschan skin color scale in order to correlate susceptibility to rickets with density of pigmentation of the skin.

Three hundred and seventy-nine Hawaiian and part Hawaiian infants under 2 years of age were also examined for the comparison of skeletal development. The diet of the Hawaiians is high in starch and lacks milk. Poi, a paste made from pounded taro root and water, is the staple Hawaiian food.

Roentgenograms.—As a preliminary step, roentgenograms were taken of the forearms, wrists and hands of twenty-seven infants under the age of 1 year in order to gain some standard for bone development and the susceptibility to rickets under the subtropical conditions in Hawaii for the various races and the varying degrees of pigmentation of the skin. Ten of these infants were Hawaiian or part Hawaiian: one boy, 4 months of age; one girl and one boy, 6 months of age; two boys, 7 months; two girls and one boy, 8 months; one boy, 10 months, and one girl, 11 months. Six infants were Filipinos; two boys, 7 months of age; one boy, 9 months; one boy, 10 months; one boy, 11 months, and one Chinese Filipino girl, 5 months. Four infants were Japanese: one girl and two boys, 6 months, and one boy, 7 months of age. Four were Porto Ricans: one girl and one boy, 7 months of age, and one boy and one girl, 8 months. Two infants were Koreans: one girl, 6 months of age and another 7 months.

Development of Muscle.—The development of muscle is closely related to skeletal development. The development of the muscle was judged by the general tone and by two simple tests for the muscles of the back and legs. After the age of 7 or 8 months, a child seated on a firm surface holds the back erect, the lumbar region is flat if the muscles of the back are well developed, but there is bulging in the lumbar region if the muscles of the back are flaccid. The muscles of the legs are tested with a child lying on his back on a firm surface. The thigh is flexed on the abdomen and if muscles are flaccid, the foot can be put over the shoulder with the leg almost parallel with the trunk, but if muscles have good tone, the leg flexes at an angle to the trunk.

Dentition.—The number of teeth present was noted at each examination in order to determine the age at which the eruption of deciduous teeth occurs. Dental caries and irregular or discolored teeth were also noted.

In earlier communications,[4] it has been pointed out that although Chinese children in Hawaii are better nourished and have better skeletal development than Chinese children in China, they have much poorer teeth. Two hundred and seventy-two of a series of 699 children in China had dental caries with rapid disintegration of the crown of the tooth, as compared with 300 of 383 Chinese children in Hawaii. In another series, among 224 girls from 6 to 22 years of age, in Chekiang Province in China, 66 per cent had good teeth and only 5 per cent had three or more carious teeth, while in Hawaii only 10 per cent of 354 Chinese girls from 6 to 20 years of age and 20 per cent of 388 Chinese boys had good teeth; and 60 per cent of the girls and 49 per cent of the boys had three or more teeth decayed or already extracted. Even in China, however, dental caries was found in 14 per cent of the children, aged 3 years, who were examined, 25 per cent of the children, aged 4 years, and 43 per cent in the children aged 5 years; so beginning caries must be sought before the age of 3 years.

RESULTS

Weight.—Table 1 gives the number of infants whose initial examination was made at each age, the total number of infants weighed and the average weight of all infants at each age. The data for Japanese male and female infants and Filipino male and female infants are given separately. The average weight for the four groups is shown graphically in the chart, which is plotted in the form of a point-to-point curve.

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4. Appleton, V. B.: Growth of Chinese, Am. J. Dis. Child. **30**:43 (July) 1925; Further Study of Growth of Chinese, China M. J. **40**:259 (March) 1926; Growth of Kwangtung Chinese in Hawaii, Am. J. Physiol. Anthrop. **11**:473 (April-June) 1928.

Before the age of 6 months, the average weight of both male and female Japanese infants is nearly the same as that of the average weight of infants of European ancestry, but after 6 months the average weight of the Japanese infants is considerably less. The average weight of Filipino infants is slightly less than that of Japanese infants at the age of 1 month, and the difference between the two becomes greater with increasing age. The weight of Filipino female infants especially lags below that of Japanese female infants from 4 to 8 months and from 13 to 18 months of age. The growth curve is similar in the two races, although its peculiarities may be more accentuated in the more poorly nourished. It differs from the growth curve of the races whose

TABLE 1.—*Weight (in Pounds) of Japanese and Filipino Infants*

	Japanese Male Infants			Japanese Female Infants			Filipino Male Infants			Filipino Female Infants		
	No. of Cases			No. of Cases			No. of Cases			No. of Cases		
Age in Mos.	New 650	All Observations 2,520	Average Weight	New 541	All Observations 2,046	Average Weight	New 419	All Observations 1,844	Average Weight	New 450	All Observations 1,879	Average Weight
1	76	76	10.006	82	82	9.618	72	72	8.920	76	76	8.692
2	104	160	12.211	64	128	11.421	52	103	10.951	69	116	10.519
3	69	193	13.825	62	156	12.989	51	124	12.350	36	130	11.966
4	58	201	15.251	41	159	14.112	25	122	13.648	27	120	13.031
5	50	213	16.218	31	154	15.235	32	136	14.815	30	132	13.734
6	39	209	16.817	35	152	15.986	21	125	15.609	33	137	14.527
7	31	194	17.404	31	154	16.536	24	128	15.857	23	128	14.817
8	24	182	18.067	25	142	17.140	17	122	16.701	15	115	15.523
9	27	168	18.228	15	118	17.480	21	123	17.139	22	119	16.514
10	27	151	18.739	21	115	17.838	10	106	17.576	23	122	16.506
11	13	133	19.414	16	101	18.263	15	107	17.989	16	106	16.940
12	18	118	20.173	19	92	18.789	18	108	18.441	12	95	17.756
13	20	102	20.330	15	78	19.388	7	79	18.709	19	91	17.868
14	13	88	20.940	13	68	19.618	6	76	19.112	9	78	17.950
15	21	84	21.114	14	70	19.953	8	63	19.165	5	75	18.235
16	12	64	21.760	10	62	20.928	9	63	19.990	6	58	18.384
17	11	59	21.912	8	55	21.210	8	54	20.412	13	60	18,798
18	15	54	22.308	9	60	21.693	10	71	20.808	5	59	19.484
21	17	46	23.360	14	52	22.633	6	43	21.972	6	45	20.758
24	14	25	25.095	16	48	23.729	7	19	23.207	5	17	21.993

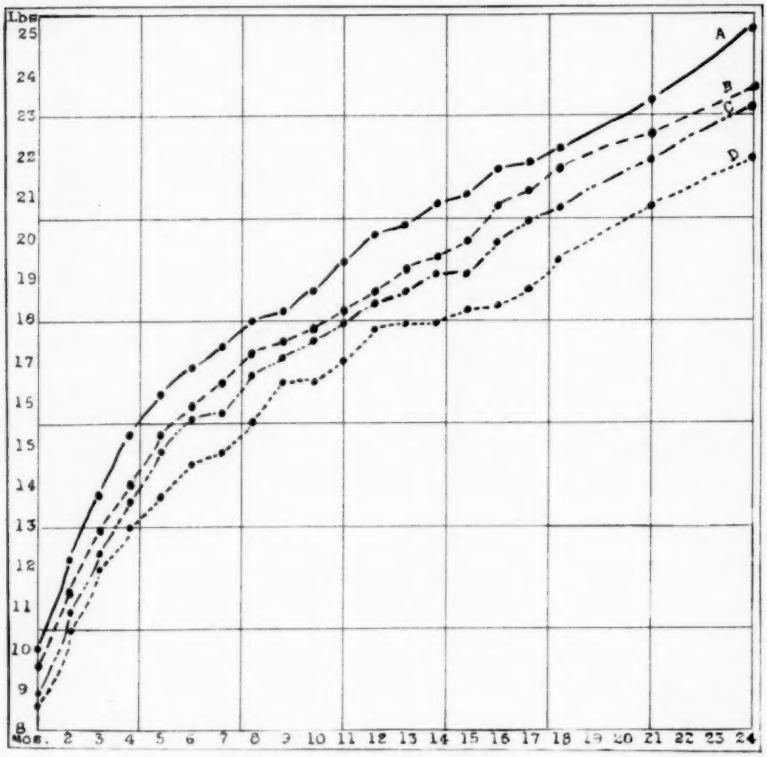
diet contains milk in that it is flattened by retardation from the end of the first six months onward, and appears to be characteristic of growth in the races whose diet contains abundant cereal and no milk.

The frequency distribution of all weights at each age in half pound intervals was considered for each age group up to the age of 12 months. The weights of both male and female Filipino infants gave a frequency curve which skews toward maximum weight the first three months, but after the age of 5 months the frequency curve tends to skew toward minimum weight. The frequency distribution of the weights of Japanese infants does not show this tendency to skew curves and malnutrition.

Gain in Weight.—The average gain in weight is shown in table 2 by the month, quarter and half year during the first twelve months of life. Both Japanese and Filipino infants show an average gain of 2 pounds

(0.9 Kg.) or more between the ages of 1 and 2 months. They show an average gain of from 1¼ (0.6 Kg.) to 1¾ (0.8 Kg.) pounds between the ages of 2 and 3 months, and a monthly gain of from ¾ (0.3 Kg.) to 1½ pounds (0.7 Kg.) between the ages of 3 and 6 months, and from ½ to ¾ pounds (0.2 to 0.3 Kg.) each month between the ages of 6 and 12 months. Males gain slightly more than females.

The average monthly gain of Japanese infants decreases with age up to 9 months and then increases slightly between the ages of 10 to 12



Weight of Japanese and Filipino infants in pounds; *A*, Japanese male infants; *B*, Japanese female infants; *C*, Filipino male infants; *D*, Filipino female infants.

months. This increase is greater for boys than for girls. The average monthly gain of Filipino infants decreases similarly up to the age of 7 months and then shows an ill defined tendency downward. This difference between the two races after the age of 6 months may be due to a difference in the ability of the mothers to suckle the infants and the consequent difference in the amount of supplementary food taken.

At first glance, it may seem surprising that Filipino infants gain almost as fast as Japanese infants when clinically they are much more

poorly nourished, but an undernourished child has to gain more rapidly than a healthy child to approach his optimum weight. This was found to be the case for both male and female Japanese infants. They were divided roughly into three groups according to the initial weight in order to compare the average gain of small thin infants, infants of medium weight and heavy infants. The gain of the small infants tends to be the greatest.

The frequency distribution of the monthly gain in weight was considered in 4 ounce (0.1 Kg.) intervals for each month up to the age of 1 year. The frequency curve skews toward the minimum gain after the age of 3 months for the Filipinos and after the age of 5 months for the Japanese.

TABLE 2.—*Monthly Increase in Weight in Pounds*

Age in Months	Japanese Male Infants		Japanese Female Infants		Filipino Male Infants		Filipino Female Infants	
	No. of Observations 1,412	Average Gain	No. of Observations 1,080	Average Gain	No. of Observations 1,061	Average Gain	No. of Observations 917	Average Gain
1 to 2	55	2.126	64	1.665	49	2.036	47	1.847
2 to 3	115	1.715	89	1.583	64	1.570	76	1.506
3 to 4	127	1.342	102	1.239	80	1.409	76	1.144
4 to 5	134	1.045	96	1.047	87	1.125	77	1.025
5 to 6	136	0.817	90	0.787	91	0.900	76	0.880
6 to 7	134	0.741	102	0.679	91	0.699	78	0.633
7 to 8	123	0.613	92	0.534	85	0.762	67	0.653
8 to 9	100	0.521	75	0.515	77	0.646	61	0.590
9 to 10	96	0.524	62	0.534	75	0.612	66	0.616
10 to 11	73	0.601	63	0.582	71	0.513	67	0.600
11 to 12	65	0.710	57	0.593	71	0.654	55	0.522
3 to 6	83	3.163	61	2.795	58	3.322	63	2.768
6 to 9	82	1.714	63	1.650	71	1.810	44	1.369
6 to 12	43	3.463	27	3.222	39	3.285	23	2.758
9 to 12	49	1.555	38	1.603	52	1.393	41	1.331

SKELETAL DEVELOPMENT

Roentgenograms.—The twenty-seven roentgenograms taken show that carpal centers of ossification develop early in Hawaii in infants of all races, and are especially early in Hawaiian infants. All ten Hawaiian infants, even a male of 4 months, showed at least two well defined carpal centers, although the appearance is said to be later in males than in females; a male infant, aged 7 months, had also the radial center, a male infant, aged 10 months, had two carpal centers and the radial center, and a Hawaiian female, aged 11 months, showed four carpal centers and the radial center.

All but one of the infants in the remaining cases had two carpal centers; this was a Japanese male infant, aged 6 months, who had one carpal center. A Japanese male infant, aged 7 months, had two carpal centers and the radial center.

The presence of rickets was not demonstrable in any of the roentgenograms taken, and only one of the infants later gave clinical signs

of rickets; this was a Porto Rican male infant who, two months after the roentgenogram had been taken, at the age of 11 months, showed flaccid muscles of the legs and back and a slight rachitic rosary, but otherwise a well formed chest. Goldberger and Mellon [5] pointed out that the appearance of carpal centers in infants with rickets is later than in infants free from rickets.

Clinical Evidence of Rickets.—Sixteen of the 1,200 Japanese infants examined showed a rachitic rosary. In all these infants, the beading of the ribs was very slight, and in five it was the only sign of rickets. Eight had flaccid muscles as well as beading, and three developed Harrison's groove subsequently. Nineteen had flaccid muscles of the back and legs without beading, thirteen had Harrison's groove without rachitic rosary, five of these showed distinct flaring of the ribs, one had pigeon breast and three had extremely flat chests.

Eleven other infants had extremely flat chests with the shafts of the ribs so poorly calcified that, when the child lay on his back, the sternum could easily be pressed down a considerable distance. These chests differ in form from the usual round infantile type and more nearly approach the adult male form, as they have a broad lateral diameter and short anteroposterior diameter. The borderline between normal and pathologic is not sufficiently well defined to permit exact percentages, but a large proportion of the Japanese infants showed a tendency to have soft flexible ribs and a broad flat chest at the age of 9 or 10 months, even when they were otherwise well developed.

Only one case of craniotabes was found; this was in an infant aged 1 month, who weighed only $7\frac{1}{16}$ pounds (3.21 Kg.), was poorly nourished and may have been born prematurely. This child did not show evidence of craniotabes at the age of 3 months. As a rule, the skulls were firm and well calcified; the fontanels were small and closed early. No Japanese child was found to have the fontanel open as late as 18 months of age.

Thirty-four of the 869 Filipino infants had rachitic rosary. In all of these the beading was very moderate, and in eleven it was the only sign of rickets. Eighteen of the infants, who had beading of the ribs, also had flaccid muscles, ten later developed Harrison's groove and five had badly formed chests. Six had Harrison's groove but no rosary, and three had pigeon breast. One child, who at the age of 11 months had rosary, Harrison's groove and flaccid muscles, at 18 months had an open fontanel with a prominent brow. One had broad wrists at the age of 10 months, together with Harrison's groove, flaccid muscles, a poorly formed chest and a flaring margin of the ribs.

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5. Goldberger, J. H., and Mellon, J.: Is the Development of the Carpal Centers Delayed in Rickets? Am. J. Dis. Child. **31**:58 (Jan.) 1926.

Thirty-five of the 379 Hawaiian infants examined had a slight beading of the ribs; ten of these were without other signs of rickets. Twenty of those who had beading also had flaccid muscles, thirteen of these also had Harrison's groove, and eleven had a poorly formed chest, three of whom had a definite pigeon breast. Nine had Harrison's groove without beading, six of these also had flaccid muscles and three had poorly formed chests.

Both the roentgenograms and the clinical observations show rickets to be rare in Hawaii and of an extremely mild type when it does occur. The ultraviolet rays of the sun in these subtropical islands are sufficient to protect children against rickets, even when the diet is inadequate. Filipino infants are slightly less well protected than Japanese, and Hawaiian infants are less well protected than either of the other two races. This slightly greater susceptibility of Hawaiian infants to rickets is associated with rapid growth, early development of bone and also with more deeply pigmented skin. Compared with the von Luschan scale, the skin color of the Japanese infants ranged from numbers 11 to 15 on the scale, with number 12 the most frequent color; the skin color of the Filipino infants ranged from 11 to 22, with 15 the most frequent color, and few darker than 18; and the skin color of the Hawaiian infants ranged from 11 to 23, with 17 as the most frequent color.

It is interesting to find a tendency to poor calcification of the shafts of the ribs, with resulting changes in the form of the chest in a race in which typical rachitic changes in the epiphyses of the long bones are rare. The same condition was even more striking in Chinese children. The presence of rickets is considered rare among Chinese infants in China, but Harrison's groove, with a flaring margin of the ribs, was almost universal in the preschool children I examined in China; 60 per cent of the girls, aged 6 years, whom I examined in Chekiang Province in China, showed poor development of bones, with resulting deformity of the chest. The percentage decreased with age up to early adolescence, which shows that nature tends gradually to compensate for the retarded calcification of the shaft of the ribs.

Hess [6] described softening of the ribs, which was associated preeminently with the atrophic infant in contradistinction to the well nourished infant who develops rickets. He considered this softening in many cases nonrachitic, and found that it was not alleviated by prolonged treatment with the two antirachitic treatments, cod liver oil and ultraviolet irradiation. The growth in weight is slow in Japanese infants during the last half of the first year; softening of the ribs develops

6. Hess, A. B.: Nonrachitic Softening of the Ribs in Infants and Children, Am. J. Dis. Child. **28**:568 (Nov. 1924.

several months after this retardation begins. The question arises why faulty calcification should affect chiefly the epiphyses in rapidly growing infants and be sensitive to ultraviolet rays, while in slowly growing infants it involves the shaft and is much less influenced by ultraviolet irradiation. It suggests that softening of the ribs may be due to an actual deficiency in calcium, possibly the result of the increased demand for calcium by rapidly successive pregnancies in the Japanese, who have an extremely high birth rate.

Dentition.—Four months was the earliest age at which two teeth were observed among Japanese and 5 months among Filipino infants, but the number of infants who had two teeth before the age of 6 months was small. From 6 to 9 months among the Japanese infants and from 7 to 10 months of age among the Filipino infants, two teeth were found more frequently than any other number. The presence of two teeth was more frequent at 8 months than at any other age in the Japanese, and at 9 months in the Filipino infants.

Five months was the earliest age at which four teeth were present among the Japanese and 6 months among the Filipino infants, but the number of instances was small before the age of 8 months. Four teeth was the most frequent number of teeth found at the age of 10 months for the Japanese and 11 months for the Filipino infants, and four teeth were present more frequently at these ages than at any other age.

The earliest age at which six teeth were present was 5 months for the Japanese and 6 for the Filipino infants, but the number of instances was small until the ages of 8 and 9 months, respectively. Six teeth were present more frequently at the age of 11 months than at any other age among the Japanese and at 12 months among the Filipino infants.

Seven months was the earliest age at which eight teeth were present in the Japanese and 8 months in the Filipino infants, but the number of infants who had eight teeth before the age of 10 months was small. From the ages of 12 to 15 months among the Japanese and from 12 to 16 months among the Filipino infants, eight teeth was the most frequent number. Eight teeth were present at the age of 12 months for the Japanese infants more frequently than at any other age, and at 14 months for the Filipino infants.

Sixteen teeth were present as early as at the age of 12 months among the Japanese and 15 months among the Filipino infants. Twelve was the most frequent number of teeth from the ages of 16 to 23 months among the Japanese and from 18 to 24 months among the Filipino infants.

Twenty teeth were found earliest at the age of 16 months in the Japanese and at 21 months in the Filipino infants. More Japanese infants had twenty teeth at the age of 24 months than any other number.

These data show that the eruption of temporary teeth begins early in Japanese and Filipino infants in Hawaii and is earlier for the Japanese than for the Filipinos. Dental caries was rare during this period of dentition. Disturbances of calcification appear to cause delayed dentition during the second year of life, rather than dental caries.

SUMMARY AND CONCLUSIONS

The growth and development of 1,200 Japanese and 869 Filipino infants in Hawaii were observed during the first two years of life. The diet of both races is high in rice and lacks milk, and the infants are breast fed. Three hundred and seventy-nine Hawaiian infants were also examined for skeletal development.

A diet abundant in cereal without milk is compatible with a high birth rate, moderate infant mortality and good growth of the offspring during lactation for the first five months of life, when the infants are dependent on breast milk alone, if the mother's diet includes suitable, adequate, supplementary food other than milk. After six months, when the infants have reached the age when additional food is needed, the gain in weight is not so rapid as when cow's milk is used as a supplementary food in the diet of infants.

Carpal centers develop early in the infants in Hawaii.

The subtropical location of the Hawaiian Islands provides sufficient ultraviolet rays in the sunlight to give almost complete protection against rickets, even when the diet of lactating mothers and of infants under 2 years of age does not contain milk. Rickets is extremely rare and is mild when it occurs.

The eruption of deciduous teeth occurs early in Japanese and in Filipino infants. It is earlier for the Japanese than for the Filipino infants.

CALCIUM AND PHOSPHORUS METABOLISM IN ARTIFICIALLY FED INFANTS

I. INFLUENCE OF COD LIVER OIL AND IRRADIATED MILK *

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Until recently, interest in rickets has been concerned more especially with the rôle of calcium, other elements being considered of secondary importance in the metabolic disturbance. Schabad,[1] however, early called attention to the phosphoric acid imbalance, believing that it was a more significant factor than the calcium deficiency. In a comparative study of the relation of the phosphorus of the urine and feces of normal and rachitic infants, he observed that there was a marked increase in the phosphorus of the feces in both breast-fed and artificially fed infants affected by rickets, and a corresponding decrease in the elimination through the kidneys. The normal breast-fed infants under his observation excreted 80 per cent of the ingested phosphorus through the kidney and 19 per cent through the tract; while in his normal infants who were artificially fed, 65 per cent of the ingested phosphorus was eliminated in the urine and 34 per cent in the stools. Breast-fed infants suffering from progressive rickets excreted 39 per cent of the ingested phosphorus in the stool, whereas the artificially fed, rachitic infants excreted 60 per cent. Similar observations were reported for older children. One child, aged 2½ years, who had marked rickets, eliminated twice as much phosphorus in the stool as in the urine. In cases of rickets in which the condition is improving this was reversed, approximately 75 per cent of the ingested phosphorus being excreted in the urine and 25 per cent in the stools. Similar results with rachitic children have been reported by Telfer,[2] and with rats by Yoder,[3] and Karelitz and Shohl.[4] Increasing the antirachitic potency of the diet,

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1. Schabad, J. A.: Arch. f. Kinderh. **54**:83, 1910.
2. Telfer, S. V.: Quart. J. Med. **16**:45, 1922.
3. Yoder, L.: J. Biol. Chem. **74**:321, 1927.
4. Karelitz, S., and Shohl, A. T.: J. Biol. Chem. **73**:655, 1927.

or direct irradiation with ultraviolet light in animals, decreased the elimination of phosphorus through the tract. Indeed, the work of McCollum, Simmonds, Shipley, and Park,[5] and of Sherman and Pappenheimer,[6] as well as that of Karelitz and Shohl,[4] suggests that the phosphate ion in the diet may possess a determining influence for or against the development of rickets in rats. Furthermore, the fact that the blood phosphorus is consistently lower in rachitic than in normal persons,[7] whereas the blood calcium is frequently within the normal range, would seem to indicate that the phosphorus metabolism is primarily at fault.

Telfer [8] and Findlay,[9] however, still believe that the intrinsic disturbance is related to faulty calcium metabolism, the result in part of some interference with the normal absorption of the calcium salts from the tract. Recent work by Murdock [10] seems to corroborate the hypothesis of a calcium deficiency. The ingestion of sodium acid phosphate increased the blood phosphorus in both normal and rachitic children, whereas the ingestion of calcium lactate and sodium acid phosphate decreased the blood phosphate in both groups; more marked results were obtained with rachitic children, the result, apparently, of a decrease of the available phosphorus in the tract. The author concludes that in active rickets there is not necessarily any defect in the absorption of phosphorus, but that the disturbance is related rather to a defective absorption of calcium. "The fixation of phosphorus in the skeleton is dependent on that of calcium, and in a disturbance with regard to the mineral elements, the absorption of an excess of phosphorus is followed by its excretion in the urine." [8]

In an investigation of the influence of different types of artificial feeding mixtures on the retentions of calcium and phosphorus in normal infants, the marked difference in the retentions of calcium and phosphorus and the relative proportion of phosphorus excreted in the urine and feces on some of the feeding mixtures suggested that through such studies early metabolic changes, which ultimately develop into rickets, may be detected. The data, furthermore, seem to indicate that in infants receiving modifications of cow's milk, rickets is related in part to physiologic changes incident to defective absorption of calcium, the result of

5. McCollum, E. V.; Simmonds, N.; Shipley, P. G., and Park, E. A.: J. Biol. Chem. **47**:507, 1921.

6. Sherman, H. C., and Pappenheimer, A. M.: J. Exper. Med. **34**:189, 1921.

7. Howland, J., and Kramer, B.: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

8. Telfer, S. V.: Quart. J. Med. **17**:245, 1923-1924.

9. Findlay, L.: Underlying Cause in Pathogenesis of Rickets, J. A. M. A. **83**:1473 (Nov. 8) 1924.

10. Murdoch, G.: Arch. Dis. Childhood **2**:285 (Oct.) 1927.

a deficiency of so-called vitamin D. The composition of the feeding mixture, however, seems to play some part.

The feeding mixtures studied have included simple dilutions of cow's milk with added dextrimaltose or lactose. These were "sterilized" by pasteurization or by the quick boiling method. The influence of added cod liver oil and of irradiated olive oil, as well as the effects of irradiation of the milk, has been tested. With the exception of one case of well developed rickets in a child 2½ years of age the data herein reported include only those obtained on seemingly normal infants; these were from 2 to 9 months of age. Up to the time the infants were used for the metabolic studies they had received feedings of boiled milk with the carbohydrate modifications as stated. Some of the infants had been given cod liver oil prior to but not during the metabolism period, while in other cases the cod liver oil, which had been given from early infancy, was continued throughout the period. A small group had not received any cod liver oil. Each metabolism study covered a period of three days. The feeding mixtures to be tested, however, were given at least three days, and in many cases for much longer periods, before the quantitative collection of stools and urine. Creatinine determinations were made on each twenty-four hour urinary excretion in order to check the completeness of the collection. The stools were marked off with carmine and carbon, or with carmine only. Data on loose stools or on stools which were not of a uniform consistency have not been included in this report.

The preparation of the feeding mixtures, the general care of the infants and the methods of analysis [11] were the same as those reported in a previous communication.[12] Seventy-four different metabolic studies are reported. These have been tabulated (1) according to the treatment of the feeding mixtures, and (2) according to the average creatinine output of the infants in the various groups, since creatinine seems a more accurate measure of physiologically functioning tissue than weight. The retention values for calcium and phosphorus, however, have been recorded for each child on the basis of weight, since this is the more usual method.

The consistently high fecal phosphorus in those infants who received the feeding of pasteurized and boiled milk (tables 1 and 2, groups A) compared with those who received the pasteurized and boiled milk to

11. The phosphorus determinations on the urine in the simple series of pasteurized and boiled milk feedings were made according to the method outlined in Hawk, P. B.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Company, ed. 8, 1923, p. 581. A change to Neumann's procedure with the Brigg's modification of the method of Bell and Doisey was made in the series in which cod liver oil and irradiated feeding were instituted. (J. Biol. Chem. **53**:13, 1922.)

12. Daniels, A. L., and Stearns, G.: J. Biol. Chem. **61**:225, 1924.

TABLE 1.—*Percentage of Ingested Calcium and Phosphorus Excreted in the Stools and Urine of Infants Receiving Pasteurized Milk Feedings*

Range of Creatinine, Mg.	Number of Infants	Average Age		Average Weight, Kg.	Average Creatinine, Mg.	Average per Cent of Ingested Calcium Excreted		Average per Cent of Ingested Phosphorus Excreted	
		Months	Days			Urine	Feces	Urine	Feces
Group A—Pasteurized Feeding									
50-60	1	2	26	4.450	57	3.96	100.31	41.58	51.61
70-80	6	6	8	6.448	77	2.89	94.84	50.47	44.28
80-90	2	5	21	5.975	84	3.27	86.60	53.56	44.42
Average	5	5	23	6.121	76	3.04	93.83	50.41	43.33
Group B—Cod Liver Oil Given Prior to Metabolism Period									
50-60	1	3	21	5.585	57	5.44	74.71	49.36	27.14
60-70	1	3	19	5.595	63	2.13	71.25	46.65	18.48
70-80	2	3	23	6.600	73	7.49	81.63	55.33	23.12
Average	3	3	22	6.095	66	5.02	77.30	51.66	22.97
Group C—Cod Liver Oil Given Prior to and During Metabolism Period									
60-70	3	3	16	5.670	64	3.83	70.78	47.86	21.74
70-80	3	4	10	6.850	75	7.09	69.06	52.49	19.70
Average	3	3	27	6.260	69	5.50	69.92	50.26	20.68

TABLE 2.—*Percentage of Ingested Calcium and Phosphorus Excreted in Stools and Urine of Infants Receiving Boiled Milk Feedings*

Range of Creatinine, Mg.	Number of Infants	Average Age		Average Weight, Kg.	Average Creatinine, Mg.	Average per Cent of Ingested Calcium Excreted		Average per Cent of Ingested Phosphorus Excreted	
		Months	Days			Urine	Feces	Urine	Feces
Group A—Boiled Feeding									
50-60	1	3	4	4.620	57	2.67	89.74	45.14	42.88
60-70	1	4	10	5.220	68	6.85	82.10	50.48	42.02
70-80	8	6	23	6.895	76	2.35	86.17	46.53	43.50
80-90	3	6	29	6.830	83	3.59	81.78	48.46	40.54
90-100	1	7	18	8.735	90	2.43	85.15	44.52	38.30
Average	6	6	13	6.730	77	2.90	85.08	46.92	42.35
Group B—Cod Liver Oil Given Prior to Metabolism Period									
50-60	4	3	10	4.953	56	6.15	74.09	58.20	25.08
60-70	6	3	24	5.424	63	3.89	69.67	47.26	27.87
70-80	6	4	17	6.057	74	4.57	79.19	52.75	25.28
Average	3	3	29	5.544	65	4.68	75.96	51.91	26.20
Group C—Cod Liver Oil Given Prior to and During Metabolism Period									
60-70	5	3	19	5.835	66	3.66	60.86	53.57	17.25
70-80	4	4	..	6.511	74	3.57	66.04	49.20	24.12
80-90	6	4	11	7.154	83	5.73	69.60	52.80	23.60
90-100	1	4	13	7.470	91	5.14	72.99	60.81	24.34
110-120	1	7	21	9.960	112	4.45	75.69	57.54	33.79
Average	4	4	2	6.268	78	4.54	67.13	52.93	22.87
Group D—Rachitic Child									
56	1	2 yr.	7 mo.	6.760	56	1.72	100.11	22.48	72.19

which cod liver oil was added (tables 1 and 2, groups B and C), is noteworthy, especially in view of the fact that the infants in all groups seemed normal and had none of the clinical symptoms of rickets. On both mixtures of simple pasteurized and boiled milk, averages of 43.33 and 42.35 per cent of the total phosphorus ingested were eliminated in the feces. These figures are fairly comparable with those reported by both Schabad [1] and Telfer [13] in studies of the early stages of rickets, and suggest that at this time the children under our observation were in the prerachitic stage. Up to the time of the metabolic study, these infants had not received any cod liver oil. The fact that cod liver oil was added subsequently in those few cases which continued under our care, in all probability prevented the development of the characteristic rachitic symptoms, and therefore led us to conclude that these infants

TABLE 3.—*Percentage of Calcium and Phosphorus Excreted in Stools and Urine of Infants Receiving Irradiated Feedings* *

Range of Creatinine, Mg.	Number of Infants	Average Age		Average Weight, Kg.	Average Creatinine, Mg.	Average per Cent of Ingested Calcium Excreted		Average per Cent of Ingested Phosphorus Excreted	
		Months	Days			Urine	Feces	Urine	Feces
Group A—Irradiated Olive Oil *									
60–70.....	2	4	6	6.360	74	6.93	56.92	54.83	13.09
Group B—Irradiated Milk									
50–60.....	1	2	25	5.422	65	6.99	57.05	59.02	19.49
70–80.....	2	5	17	7.283	77	3.48	71.61	37.91	26.60
80–90.....	1	5	20	6.865	80	1.66	72.30	56.99	23.68
90–100.....	1	5	28	7.110	91	7.39	42.05	61.72	9.12†
Average.....	5	3		6.792	78	4.47	64.20	57.17	22.21

* The oil was exposed in a thin layer of about ⅛ inch (3.17 mm.) in thickness at a distance of 2 feet (60.8 cm.) for thirty minutes.

† This study was made during July. During June and July this infant had been exposed daily to the direct rays of the sun.

were normal. This part of the study was made before the antirachitic properties of cod liver oil were appreciated. The oil was being used at this time merely as a means of increasing the vitamin A content of the feeding mixtures.

The addition of cod liver oil to the feedings of pasteurized and boiled milk resulted in much lower values for fecal phosphorus, the infants in each group receiving the cod liver oil during the metabolism period averaging 20.68 and 22.87 per cent, respectively, while for those infants who received the cod liver oil prior to but not during the metabolism period the averages were 22.97 and 26.2 per cent of the ingested phosphorus. The two infants who were given the irradiated olive oil (table 3, group A) eliminated the lowest amount of phosphorus (13.09 per cent) by way of the tract. The average figures for the feedings of irradiated milk were comparable with those for the

13. Telfer, S. V.: Quart. J. Med. **14**:45, 1922.

feedings of boiled milk and cod liver oil. In marked contrast to these is the amount (72.19 per cent) of ingested phosphorus eliminated through the tract in the one rachitic child (R. W.) included in the study (table 2, group D).

With the exception of this rachitic child, who eliminated only 22.48 per cent of the ingested phosphorus through the kidneys, the percentage of the ingested phosphorus excreted in the urine varied only slightly. The lowest average, 46.92 per cent, was obtained with the simple feedings of boiled milk, and the highest, 57.17 per cent, on the mixtures of irradiated milk. In all groups, the percentage of phosphorus excreted in the urine seemed within the normal range. With the exception of the mixture of irradiated milk, in which slightly higher percentages were found, the variations among the different groups were not any greater than those within the groups.

The amount of phosphorus retained on the feeding mixtures tested appears to be related directly to the amount absorbed. The lowest retentions (averaging 0.0075 and 0.0115 Gm. per kilogram, respectively) were obtained among the simple feedings of pasteurized and boiled milk (tables 4 and 5, groups A). The highest retentions (averaging 0.0315 Gm. per kilogram) were found in the two feedings of irradiated olive oil (table 6, group A). Among the feedings of cod liver oil and irradiated milk there was considerable uniformity in the amount retained as well as in the percentage excreted through the tract. The average retention in the two groups in which pasteurized milk and cod liver oil were given was 0.0282 and 0.0297 Gm. per kilogram, respectively (table 4, groups B and C), and in the two groups in which boiled milk and cod liver oil were given the average retention was 0.0220 and 0.0242 Gm. per kilogram, respectively (table 5, groups B and C). The retention for the rachitic infant, 0.0064 Gm. per kilogram, was more nearly comparable to the retentions of the infants receiving the simple feedings of pasteurized milk (average 0.0075 Gm. per kilogram, table 4, group A).

The amount of calcium eliminated by way of the tract seemed to be influenced both by the method of sterilizing the feeding mixture and by its antirachitic potency, the latter having by far the greater influence. On the simple feedings of pasteurized milk an average of 93.83 per cent of the ingested calcium was eliminated by way of the tract; whereas, on the simple feeding of boiled milk an average of 85.08 per cent was so eliminated (tables 1 and 2, groups A). In the two groups receiving the feedings of pasteurized milk and cod liver oil, there was an average of 77.3 and 69.89 per cent, respectively, of the ingested calcium eliminated in the feces (table 1, groups B and C). In the two groups in which boiled milk and cod liver oil were given an average of 75.96 and 67.13 per cent, respectively, was eliminated (table 2,

TABLE 4.—*Calcium and Phosphorus Retentions in Infants Receiving Pasteurized Milk Feedings*

Name	Age: Month	Age: Days	Weight, Kg.	Creatinine, Mg.	Calcium: Ingestion, Gm.	Calcium: Excretion: Urine, Gm.	Calcium: Excretion: Feces, Gm.	Calcium: Retention per Kg., Gm.	Phosphorus: Ingestion, Gm.	Phosphorus: Excretion: Urine, Gm.	Phosphorus: Excretion: Feces, Gm.	Retention per Kg., Gm.	Retention Ratio, Calcium : Phosphorus	Amount of Cod Liver Oil-Cc.
Group A—Pasteurized Feedings														
G. V.	2	26	4.450	57	0.6121	0.0243	0.6385	—0.0113	0.4999	0.2079	0.2580	0.0076	Neg.	
M. P.	6	10	6.925	77	0.9057	0.0266	0.9214	—0.0061	0.7711	0.4188	0.3796	—0.0039	Neg.	
M. P.	7	2	7.175	78	0.9628	0.0250	0.8974	0.0056	0.8069	0.4629	0.2892	0.0076	0.7	
G. G.	6	16	6.050	78	0.8457	0.0438	0.7464	0.0091	0.7108	0.3381	0.3017	0.0067	1.3	
G. G.	7	1	6.550	76	0.9028	0.0193	0.7669	0.0178	0.7545	0.4169	0.2778	0.0091	1.9	
D. W.	5	4	5.765	79	1.0540	0.0255	1.0450	—0.0028	0.8090	0.3021	0.4494	0.0099	Neg.	
D. W.	5	18	6.225	78	1.0540	0.0257	1.0528	—0.0039	0.8090	0.3840	0.3666	0.0093	Neg.	
W. A.	6	3	6.400	83	0.8467	0.0352	0.7640	0.0074	0.6546	0.3446	0.2532	0.0088	0.8	
M. I.	5	9	5.550	85	0.8467	0.0202	0.7026	0.0223	0.6546	0.3566	0.2285	0.0125	1.7	
Average	5	23	6.121	76	0.8922	0.0272	0.8372	0.0042	0.7189	0.3624	0.3115	0.0075	0.5	
Group B—Cod Liver Oil Given Prior to Metabolism Period														
L. T.	3	21	5.585	57	0.8178	0.0445	0.6110	0.0290	0.6647	0.3281	0.1804	0.0279	1.0	3.3
J. A.	3	19	5.595	63	0.8178	0.0175	0.5827	0.0388	0.6647	0.3101	0.1229	0.0414	0.9	3.3
R. W.	4	5	6.440	73	0.8178	0.0292	0.6349	0.0238	0.6647	0.3500	0.1039	0.0327	0.7	3.3
N. W.	3	12	6.760	73	0.8178	0.0934	0.7004	0.0035	0.6647	0.3856	0.2035	0.0110	0.3	3.3
Average	3	22	6.095	66	0.8178	0.0411	0.6322	0.0238	0.6647	0.3434	0.1527	0.0282	0.8	
Group C—Cod Liver Oil Given Prior to and During Metabolism Period														
W. C.	2	19	5.170	63	0.6400	0.0376	0.4202	0.0352	0.5152	0.2524	0.1097	0.0296	1.1	3.3
L. T.	3	29	5.915	64	0.8178	0.0385	0.5728	0.0349	0.6647	0.3153	0.1693	0.0304	1.1	3.3
J. A.	3	29	5.925	66	0.8178	0.0112	0.6179	0.0318	0.6647	0.3153	0.1220	0.0383	0.8	5.0
R. W.	4	16	6.590	73	0.8178	0.0325	0.6203	0.0250	0.6647	0.3398	0.1452	0.0272	0.9	3.3
N. W.	3	21	7.172	76	0.8178	0.0875	0.5392	0.0266	0.6647	0.3398	0.1336	0.0266	1.0	5.0
M. E.	4	23	6.790	77	0.7760	0.0510	0.5061	0.0322	0.6449	0.3570	0.1103	0.0261	1.2	5.0
Average	3	27	6.260	69	0.7812	0.0430	0.5460	0.0309	0.6364	0.3199	0.1316	0.0297	1.0	

groups B and C). It will be observed that although the addition of cod liver oil to the feedings of pasteurized milk materially decreased the elimination of calcium through the tract, the percentage of the ingested calcium so eliminated remained slightly higher in the two groups receiving pasteurized milk than in the corresponding groups receiving boiled milk; the lowest values in each group were obtained when the cod liver oil was given throughout the metabolism period. The slightly higher elimination values in the period in which pasteurized milk and cod liver oil were given appeared to be within the limits of error, but when these are considered in relation to the other observations they may be significant. The infants who received the feedings of irradiated milk (table 3) excreted 64.2 per cent of the ingested calcium in the stool; while those who were given the irradiated olive oil excreted 56.92 per cent—the lowest in the series.

The amount of calcium retained was inversely proportional to the amount excreted in the stools, since the calcium eliminated in the urine was small and fairly comparable in all groups; the average urinary calcium in the group of infants who did not receive cod liver oil was only slightly lower than in the groups in which the oil was given. The lowest calcium retentions (averaging 0.0042 Gm. per kilogram) were obtained in the group in which pasteurized milk was given without cod liver oil (table 4, group A). Low, but considerably higher values (averaging 0.0149 Gm. per kilogram) were obtained with the infants who received the feeding of boiled milk (table 5, group A). The addition of cod liver oil as well as the irradiation of the milk greatly increased the amount of calcium retained, the figures in many cases being comparable to the high values reported for breast-fed infants. The averages in the two groups in which the feedings consisted of pasteurized milk and cod liver oil, however, were lower than in the corresponding groups in which boiled milk was given. When the cod liver oil was given prior to but not during the metabolism period, the average retentions were 0.0238 Gm. per kilogram for the group in which pasteurized milk was given and 0.0274 Gm. per kilogram for the group in which boiled milk was given (tables 4 and 5, groups B, respectively). With the infants receiving the cod liver oil throughout the metabolism period there was an average retention of 0.0309 Gm. per kilogram for the group in which pasteurized milk was given and 0.0357 Gm. per kilogram for the group in which boiled milk was given (tables 4 and 5, groups C).

It will be noted that there is much less constancy within the groups receiving the cod liver oil prior to the metabolism period than among those who were given the cod liver oil prior to and during the metabolism period. These variations are what would be expected in view of the fact that the oil was omitted for different periods of time before the

TABLE 5.—*Calcium and Phosphorus Retentions in Infants Receiving Boiled Milk Feedings*

Name	Age		Weight, Kg.	Creatinine, Mg.	Calcium				Phosphorus				Retention Ratio, Amount Calcium :	
					Ingestion, Gm.	Excretion		Retention per Kg., Gm.	Ingestion, Gm.	Excretion		Retention per Kg., Gm.	of Cod Liver Oil-Ce.	
	Month	Days				Urine, Gm.	Feces, Gm.			Urine, Gm.	Feces, Gm.		Phosphorus	
Group A—Boiled Feedings														
G. V.	3	4	4.620	57	0.6121	0.0164	0.5493	0.0100	0.4999	0.2257	0.2144	0.0129	0.7	
R. C.	4	10	5.220	68	0.7464	0.0512	0.6128	0.0157	0.5742	0.2899	0.2413	0.0082	1.9	
E. W.	7	..	8.425	73	0.8076	0.0250	0.7624	0.0023	0.6069	0.2708	0.2954	0.0048	0.4	
M. P.	6	23	7.000	77	0.9057	0.0207	0.9074	0.0032	0.7711	0.4018	0.3739	−0.0006	Neg.	
M. P.	7	7	7.350	78	0.9628	0.0236	0.8955	0.0059	0.8069	0.4306	0.2995	0.0104	0.5	
G. G.	6	24	6.400	77	0.8457	0.0147	0.6217	0.0327	0.7108	0.3403	0.2989	0.0111	2.9	
G. G.	7	12	6.700	78	0.9028	0.0224	0.6171	0.0329	0.7545	0.3081	0.2723	0.0247	1.5	
D. W.	5	10	5.950	77	1.0540	0.0257	0.9036	0.0209	0.8090	0.3525	0.3701	0.0145	1.4	
D. W.	5	25	6.475	78	1.0540	0.0252	0.9162	0.0173	0.8090	0.3576	0.3675	0.0129	1.3	
D. W.	7	23	6.860	77	0.9607	0.0199	0.8333	0.0156	0.7632	0.3453	0.3464	0.0104	1.5	
G. G.	8	26	7.790	83	0.9607	0.0433	0.8314	0.0110	0.7632	0.3599	0.3435	0.0076	1.4	
W. A.	6	11	6.500	80	0.8467	0.0288	0.6940	0.0206	0.6546	0.2666	0.2871	0.0109	1.8	
M. I.	5	20	6.200	86	0.8467	0.0233	0.6455	0.0286	0.6546	0.3478	0.2096	0.0156	1.8	
A. T.	7	18	8.735	90	1.0186	0.0248	0.8674	0.0144	0.7775	0.3462	0.2978	0.0152	0.9	
Average	6	13	6.730	77	0.8946	0.0260	0.7612	0.0149	0.7111	0.3337	0.3012	0.0115	1.2	
Group B—Cod Liver Oil Given Prior to Metabolism Period														
H. S.	3	16	4.820	55	0.6400	0.0352	0.3807	0.0464	0.5152	0.2868	0.0937	0.0279	1.6	3.3
H. H.	2	23	4.670	55	0.5886	0.0402	0.4436	0.0224	0.4759	0.2589	0.1142	0.0220	1.0	3.3
H. H.	3	5	4.875	56	0.6971	0.0355	0.5328	0.0264	0.5318	0.2844	0.1627	0.0173	1.5	3.3
H. H.	3	26	5.450	59	0.7028	0.0507	0.5905	0.0113	0.5235	0.3629	0.1426	0.0038	2.9	3.3
W. C.	2	12	5.000	61	0.6400	0.0290	0.3528	0.0516	0.5152	0.2737	0.0885	0.0306	1.6	3.3
R. O.	7	10	6.875	62	0.9257	0.0357	0.6352	0.0370	0.6959	0.3023	0.1635	0.0334	1.1	3.3
R. S.	3	19	5.250	63	0.6928	0.0162	0.4924	0.0350	0.5942	0.2703	0.2300	0.0180	1.9	3.3
R. S.	3	24	5.400	64	0.6928	0.0131	0.5845	0.0176	0.5942	0.2710	0.2529	0.0133	1.3	3.3
J. B.	2	20	5.030	64	0.6286	0.0257	0.5083	0.0186	0.4803	0.2420	0.1478	0.0179	1.0	3.3
R. R.	3	3	4.990	67	0.6400	0.0452	0.3669	0.0456	0.5152	0.2451	0.0636	0.0413	1.1	3.3
J. C.	3	8	5.150	71	0.6971	0.0452	0.5657	0.0167	0.5318	0.2781	0.1647	0.0172	0.9	3.3
R. S.	5	11	6.400	73	0.8357	0.0145	0.7516	0.0108	0.6143	0.3264	0.1896	0.0153	0.7	3.3
R. S.	5	26	6.850	73	0.9000	0.0178	0.7752	0.0156	0.6663	0.3331	0.1963	0.0199	0.8	3.3
R. S.	5	5	6.395	74	0.8357	0.0195	0.6500	0.0259	0.6143	0.3385	0.1493	0.0197	1.3	3.3
J. C.	3	21	5.550	76	0.6928	0.0545	0.4407	0.0356	0.5313	0.2839	0.0940	0.0276	1.2	3.3
Average	3	29	5.544	65	0.7234	0.0339	0.5395	0.0232	0.6034	0.3189	0.1071	0.0282	0.8	3.3
J. C.	4	3	6.000	78	0.7657	0.0648	0.5612	0.0274	0.5328	0.2922	0.1475	0.0220	1.2	

Group C—Cod Liver Oil Given Prior to and During Metabolism Period														
J. M.	1	28	5.400	62	0.7392	0.0317	0.4771	0.0426	0.5796	0.2886	0.1430	0.0274	1.5	5.0
E. M.	2	13	5.650	66	0.7930	0.0315	0.3831	0.0663	0.6279	0.3605	0.0648	0.0358	1.8	5.0
J. A.*	4	6	6.255	67	0.8178	0.0119	0.5743	0.0370	0.6642	0.3307	0.1375	0.0313	1.1	5.0*
W. C.	3	5	5.800	67	0.6928	0.0309	0.3957	0.0448	0.5314	0.2908	0.0744	0.0286	1.5	5.0
E. M.	2	24	6.070	69	0.7930	0.0287	0.5076	0.0423	0.6279	0.3535	0.1035	0.0281	1.5	5.0
E. M.	3	9	6.575	72	0.7930	0.0385	0.5371	0.0330	0.6279	0.3430	0.1318	0.0232	1.4	5.0
P. H.†	2	10	6.150	73	0.8008	0.0304	0.4755	0.0479	0.6780	0.2196	0.1580	0.0439	1.0	5.0†
R. W.	4	24	6.276	75	0.7789	0.0270	0.5197	0.0369	0.6331	0.3500	0.1330	0.0239	1.5	3.3
R. C.	5	18	7.045	79	0.8634	0.0198	0.6043	0.0338	0.6762	0.3260	0.2081	0.0201	1.6	3.3
M. E.	5	..	6.850	81	0.8400	0.0511	0.4818	0.0448	0.6840	0.3805	0.1351	0.0245	1.8	5.0
P. H.	3	24	7.347	82	0.8900	0.0149	0.7072	0.0228	0.7450	0.3843	0.2396	0.0164	1.3	5.0
N. W.‡	4	1	7.605	82	0.8178	0.0812	0.4904	0.0323	0.6647	0.2756	0.1114	0.0365	0.8	5.0‡
E. M.	3	24	6.975	83	0.8659	0.0427	0.6734	0.0214	0.6762	0.3759	0.1788	0.0126	1.7	5.0
R. R.	5	11	6.900	85	0.9000	0.0700	0.0262	0.0295	0.6663	0.3854	0.1496	0.0190	1.5	5.0
E. M.	4	6	7.250	85	0.8659	0.0371	0.0258	0.0280	0.6762	0.3759	0.1639	0.0188	1.5	5.0
E. M.	4	13	7.470	91	0.9379	0.0483	0.6846	0.0274	0.7381	0.4489	0.1797	0.0145	1.8	5.0
P. H.	7	21	9.950	112	1.0540	0.0469	0.7977	0.0210	0.8211	0.4725	0.2775	0.0071	2.9	5.0
Average	4	2	6.268	78	0.8377	0.0381	0.5624	0.0357	0.6657	0.3524	0.1523	0.0242	1.48	
Group D—Rachitic Child. Serum calcium = 8.5 mg.; serum phosphorus = 1.3 mg. per 100 cc.														
D. W.	2 yr.	7 mo.	6.760	56	0.9780	0.0169	0.9791	−0.0026	0.8136	0.1829	0.5876	0.0064	Neg.	5.0

* J. A. had received feedings of boiled milk for four days before this metabolic period. Previously for a period of twenty-two days, he had been given feedings of pasteurized milk.

† P. H. had received feedings of quickly boiled milk six days before this metabolic period. Previously, he had been receiving Hoos albumin milk—a high protein super-heated milk.

‡ N. W. had received feedings of boiled milk for only four days before this metabolic period. Previously, for seventeen days, he had received feedings of pasteurized milk.

TABLE 6.—*Calcium and Phosphorus Retentions in Infants Receiving Irradiated Feedings*

Name	Age		Weight, Kg.	Creatinine, Mg.	Calcium				Phosphorus				Retention Ratio, Amount Calcium : Phosphorus	Amount of Cod Liver Oil-Cc.
					Ingestion, Gm.	Excretion		Retention per Kg., Gm.	Ingestion, Gm.	Excretion		Retention per Kg., Gm.		
	Month	Days				Urine, Gm.	Feces, Gm.			Urine, Gm.	Feces, Gm.			
Group A—Irradiated Olive Oil, 5 Cc.														
R. R.	4	22	6.350	77	0.8200	0.0700	0.4717	0.0438	0.6488	0.3702	0.0899	0.0297	1.40	
W. C.	3	20	6.370	72	0.7657	0.0400	0.4309	0.0462	0.6034	0.3165	0.0742	0.0333	1.38	
Average	4	6	6.360	74	0.7928	0.0550	0.4513	0.0450	0.6261	0.3433	0.0820	0.0315	1.40	
Group B—Irradiated Milk														
M. E.	2	25	5.422	65	0.7553	0.0528	0.4309	0.0506	0.5520	0.3258	0.1076	0.0218	2.3	5.0
J. M.	4	7	7.000	76	0.8890	0.0441	0.5663	0.0398	0.7119	0.4165	0.1461	0.0213	1.8	5.0
R. C.	6	27	7.566	79	0.9240	0.0198	0.7524	0.0200	0.7231	0.3658	0.2024	0.0125	1.6	3.3
B. C.	5	20	6.835	80	0.8624	0.0144	0.6236	0.0326	0.6748	0.3846	0.1598	0.0189	1.7	3.3
M. E.	5	28	7.110	91	0.7711	0.0570	0.3243	0.0548	0.6474	0.3996	0.0591	0.0269	2.0	5.0
Average	5	3	6.792	78	0.8403	0.0376	0.5395	0.0395	0.6618	0.3784	0.1470	0.0203	1.9	

metabolism period. These data, however, have been included primarily because of the retention ratios.

Rickets has been attributed variously to a deficiency of either calcium or phosphorus in the diet, a failure in the absorption of one or the other of these elements from the tract, or an imbalance in the calcium and phosphorus retentions. Among the metabolic studies of breast-fed and artificially fed infants there are reported enough cases in which the calcium and phosphorus retention ratio is approximately 2, for us, tentatively, to accept this as normal. The fact that this ratio has been found to exist in the blood of normal infants as well as in human milk [14] adds further weight to this hypothetic figure. Indeed, Telfer [15] stated that a slight excess of phosphorus should be retained over that required for bone formation. The calcium phosphorus retention ratio of 2 would seem to fulfil this requirement.

The calcium phosphorus retention ratios of the infants on the various feedings differed widely. With but few exceptions, on the simple mixtures of pasteurized milk the retention ratios were extremely low, averaging 0.5. Several of the infants were in negative calcium balance. On the simple feedings of boiled milk the ratios were somewhat higher, averaging 1.2. Greater variations, however, were obtained among the simple feedings of pasteurized and boiled milk than among the feedings of pasteurized and boiled milk to which cod liver oil was added.

The average ratios in the two groups in which pasteurized milk and cod liver oil were given were 0.8 and 1, respectively. According to Karelitz and Shohl,[4] retention ratios of 1 are characteristic of healing rickets, but since the infants in both groups had received cod liver oil since early infancy (18 days of age) we are loath to believe that they were in the healing stage of rickets. It seems more probable that these lower ratios on the feedings of pasteurized milk are related to a prerachitic stage, and that symptoms characteristic of mild rickets would have developed had this type of feeding been continued.

The average ratios in the groups receiving boiled milk and cod liver oil were 1.2 and 1.48, respectively. The slight variations found among these infants are perhaps what would be expected, in view of the fact that the antirachitic potency of milk differs from season to season, and that the cod liver oil used was not in all cases a pharmacologically standardized product. The amount of oil used varied somewhat. During the early part of the investigation 10 drops of oil (3.3 cc.) were added to each of seven bottle feedings; later this was changed to 15 drops (5 cc.). The retention ratios, however, do not seem to have been greatly influenced by the difference in the amount of oil used.

14. Bosworth, A. W.: J. Biol. Chem. **20**:707, 1915.

15. Telfer, S. V.: Quart. J. Med. **16**:63, 1922-1923.

Consistently high retention ratios (average Ca/P = 2) were obtained among the infants receiving the feedings of irradiated milk, and the mixtures to which irradiated olive oil [16] was added (average Ca./P = 1.48). The probable explanation for the greater uniformity here is the more constant antirachitic potency of these feeding mixtures. The milk used was irradiated in our own laboratories, and special effort was made to control the conditions during irradiation.[17]

For a child to grow normally it is probable that the calcium and phosphorus must be retained in certain definite proportions. It is also probable that there is a definite relation between the rate of growth and the amount of these elements retained. Optimum development would seem to demand the retention of optimum amounts of calcium and phosphorus in the ratio of approximately 2 parts of calcium to 1 part of phosphorus. These infants on the various types of feeding mixtures showed considerable variations in the amount of calcium and phosphorus retained as well as in the retention relationships. On the feedings of pasteurized milk without the addition of cod liver oil there was a low retention of both calcium and phosphorus, the calcium values being lower in relation to the accepted normal values than the phosphorus. On the simple feedings of boiled milk both the calcium and phosphorus retentions were higher, the average for the calcium (0.0149 Gm. per kilogram) being considerably less than one half of the value given for normal infants, while the average of the phosphorus retentions (0.0115 Gm. per kilogram) was approximately one half that reported for normal infants. The addition of cod liver oil to the feeding mixtures, or the irradiation of the milk resulted in a marked increase in the retention of both elements. The average amount of phosphorus retained in the infants to whom cod liver oil was given in addition to the milk (tables 4 and 5, groups B) was found to be comparable to the high values reported for breast-fed infants. This was found not to be the case with calcium. In the feedings of pasteurized milk to which cod liver oil was added the amount of calcium retained averaged considerably less than the optimum; while on the feedings of boiled milk and cod liver oil the average was somewhat higher than with the feedings of pasteurized milk but in many cases below the optimum. A comparison of the high values for calcium retentions on the mixtures of irradiated olive oil and irradiated milk with those of the mixtures of cod liver oil suggests that the amount of cod liver oil used in the feeding mixtures may not have been sufficient to produce the most favorable conditions of

16. For the irradiated olive oil we are indebted to Professor H. Steenbock, Department of Animal Chemistry, University of Wisconsin.

17. A ½ inch (1.27 cm.) layer of milk was irradiated by means of a mercury quartz lamp (Hanovia) at a distance of 2 feet (60.8 cm.) for twenty minutes.

absorption and retention of calcium. It is possible also that because of the nature of the feeding mixture the cod liver oil was not wholly available. The occlusion in the stool of that substance in the oil which carries the radiant energy may account for these lower retentions. The lower absorption of vitamin A in the artificially fed infant has been similarly explained.[18] Eliot [19] observed a high percentage of mild rickets among infants who had been receiving much larger prophylactic doses of cod liver oil. The less than optimum calcium- phosphorus retention ratios observed in many infants who received feeding mixtures to which cod liver oil was added would seem to be in harmony with Dr. Eliot's observations. The generally lower calcium retentions in the infants receiving the feedings of pasteurized milk even when cod liver oil was added suggest that the method of heating the milk may in some way be involved. The addition of cod liver oil greatly increased the phosphorus retentions bringing the averages somewhat higher than those of feedings of boiled milk and cod liver oil. The calcium retentions were also increased, but not sufficiently to bring the retention ratios to the accepted norm (calcium to phosphorus or calcium phosphorus $= 2$). These lower calcium retentions may be related to a decrease in the available calcium, the result of the longer heat treatment of the milk, or to other changes related to the heating processes. The milk used was pasteurized by the hold process in the individual feeding bottles, the conditions being as nearly as possible comparable to those used in the commercial process. The cod liver oil was added in all cases after the feedings were removed from the pasteurizer, thus eliminating any possibility of change incident to heating. Methods used in sterilizing or drying milk may materially affect the solubility and therefore the availability of some of its various constituents. Bosworth [20] called attention to the change in the solubility of the calcium and phosphorus in cow's milk resulting from different methods of drying, and stated the belief that this may have an important bearing on infant nutrition. However, before conclusions can be drawn regarding the value of pasteurized milk in infant nutrition, further metabolic studies should be made with the commercial product to which larger amounts of cod liver oil are added, or in which some other source of the antirachitic factor is used. It seems probable that much of the confusion in the literature regarding the availability of calcium and phosphorus in different foods is due to the fact that the antirachitic potency of the diet has not been controlled,

18. Daniels, A. L.: Proc. Soc. Exper. Biol. & Med. **13**:824, 1926.

19. Eliot, M. M.: Control of Rickets: Preliminary Discussion of Demonstration in New Haven, J. A. M. A. **85**:656 (Aug. 29) 1925.

20. Bosworth, A. W.: Infant Feeding: Chemical Studies of Certain Dry Milk Products Used in Infant Feeding, Am. J. Dis. Child. **22**:455 (Nov.) 1921.

or that the amount of exposure to ultraviolet rays of the sun has differed in the experiments. The high calcium and phosphorus retentions during the second metabolic period of infant M. E. (table 6, group B) is a case in point. The study was made during July, when the infant had been exposed daily to the direct rays of the sun.

SUMMARY

The results of the investigation indicate that in infants who receive feedings of modified cow's milk there may be a failure to absorb from the alimentary tract a sufficient amount of calcium and phosphorus to meet the physiologic requirements. Under the conditions of the investigations, the absorption of these elements was greatly influenced by the antirachitic potency of the feeding mixture. Cod liver oil in the amounts used was less effective as a means of supplying radiant energy (vitamin D) than was either irradiated olive oil or irradiated milk. A comparison of the calcium and phosphorus retentions in infants on the simple feedings of pasteurized and boiled milk with those of the high values reported for breast-fed infants shows greater differences between the calcium retentions than between the phosphorus retentions. Among the infants who received added cod liver oil there was less variation in the phosphorus retention than in the calcium retentions. This was especially noticeable among those infants receiving feedings of pasteurized milk.

Drawing conclusions from the data obtained, it seems probable that rickets is related to an imbalance in the amount of calcium and phosphorus retained. In infants receiving modifications of cow's milk, this imbalance appears to be due more frequently to a deficiency of calcium. A calcium-phosphorus retention ratio of approximately two (calcium phosphorus = 2) would seem to be normal for infants under 1 year of age. For optimum growth, infants between the ages of 2 and 9 months should retain between 40 and 50 mg. of calcium and between 20 and 25 mg. of phosphorus per kilogram of body weight. A high percentage of phosphorus in the stools of infants receiving feedings of cow's milk has been shown to be correlated with a low absorption of calcium. By determining the percentage of the ingested phosphorus in the urine and feces it is believed that early metabolic disturbances incident to the development of rickets in the infant receiving modifications of cow's milk may be detected.

TETANY IN INFANTS

A COMPARISON OF VARIOUS AGENTS USED IN TREATMENT *

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Numerous agents have been used in the treatment of infants with tetany. These may be divided into two groups: (1) substances which effect an immediate but transient rise in the serum calcium, for example, calcium chloride and parathyroid extract, and (2) those with a slower but more lasting effect, namely, ultraviolet radiant energy, irradiated cholesterol and irradiated ergosterol. It is our purpose in this paper to describe the effect of the second group of agents on the clinical manifestations and the serum calcium of infants with tetany.

ULTRAVIOLET RADIANT ENERGY

The curative effect of ultraviolet radiant energy on infants with tetany was first demonstrated by Huldschinsky [1] in 1920. Similar results were obtained by Sachs.[2] Hoag [3] and Casparis and Kramer [4] found that the clinical improvement following irradiation is accompanied by a rise in the calcium concentration of the serum from low tetanic values to normal. Kramer, Casparis and Howland [5] and Tisdall [6]

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* From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University; the Children's Medical Division and Department of Pathology, Bellevue Hospital.

1. Huldschinsky, K.: Tetanie—Die Beeinflussung der Tetanie durch Ultraviolettlicht, Ztschr. f. Kinderh. **26**:207, 1920.

2. Sachs, F.: Ultraviolet Treatment of Tetany, Jahrb. f. Kinderh. **93**:167, 1920.

3. Hoag, L. A.: Treatment of Infantile Tetany with Ultraviolet Radiation, Its Effect on Clinical Symptoms and on the Calcium Concentration in the Blood Serum, Am. J. Dis. Child. **26**:186 (Aug.) 1923.

4. Casparis, H., and Kramer, B.: The Treatment of Active Infantile Tetany with Radiation from the Mercury Vapor Quartz Lamp, Bull. Johns Hopkins Hosp. **34**:219 (July) 1923.

5. Kramer, B.; Casparis, H., and Howland, J.: Ultraviolet Radiation in Rickets, Am. J. Dis. Child. **24**:20 (July) 1922.

6. Tisdall, F. F.: Effects of Ultraviolet Rays on the Calcium and Inorganic Phosphate Content of the Blood Serum of Rachitic Infants, Canad. M. A. J. **12**:536, 1922.

had earlier noted a rise in the serum calcium of infants with rickets following ultraviolet irradiation.

The results in infants with tetany following treatment with ultraviolet radiant energy are shown in table 1. An air-cooled mercury vapor arc encased in quartz was used. The rays were passed through

TABLE 1.—*The Effect of Ultraviolet Radiant Energy on the Serum Calcium and Inorganic Phosphate of Six Infants with Tetany*

Patient	Color	Sex*	Age	Weight, Kg.	Date	Length of Treatment Days	Serum Calcium Mg. per Cent	Inorganic Phosphorus Mg. per Cent	Comment
1 C. S.	black	♂	6 mos.	6.3	4/ 4/27	0	6.1	2.1	Marked rickets; convulsions; anodal reversal; C. C. T.† 2.2
					4/ 9/27	0	...	...	Treatment started
					4/10/27	1	6.7	...	
					4/15/27	6	7.4	...	
					4/18/27	9	9.8	3.6	E. R. normal
2 B. F.	white	♀	22 mos.	9	11/16/26	0	7.1	3.4	Convulsions; carpopedal spasm, crow
					11/27/26	0	7.2	...	Treatment started without filter
					12/ 2/26	2	8.4	...	
					12/ 8/26	8	8.8	...	
					12/13/26	13	10.1	5.4	
3 V. D'A.	white	♂	16 mos.	9.5	2/23/27	2	5.6	5.2	Active Chvostek
					3/ 7/27	14	8.8	4.7	
					3/15/27	22	10.4	4.9	
4 P. E.	white	♀	5 mos.	2.9	2/ 5/27	0	6.4	3.1	Convulsions
					2/12/27	6	8.5	...	
					2/18/27	12	9.6	...	
5 N. R.	white	♀	7 mos.	7.5	2/18/27	0	5.7	...	Convulsions, crow; received 4 Gm. of calcium chloride on 2/18 and 2/19
					2/21/27	0	5.7	...	
					2/22/27	..	...	...	Treatment started
					2/23/27	1	5.8	...	
					2/26/27	4	7.2	...	
					2/28/27	6	...	...	Anodal reversal
					3/ 7/27	15	10.1	3.3	
6 T. S.	white	♂	12 mos.	10	3/29/27	0	7.0	3.2	Convulsions
					4/ 1/27	3	7.4	3.3	
					4/ 4/27	6	7.6	3.3	Anodal reversal
					4/10/27	12	9.0	3.2	E. R. normal

* In this column ♂ indicates male; ♀, female.
† In this and subsequent tables, E. R. indicates electrical reaction and C. C. T., cathodal closing tetany.

a pyrex glass filter which transmitted radiant energy down to 2,950 angstrom units. Transmission below 3,000 angstrom units was slight. The filter reduced the intensity in the ultraviolet portion of the spectrum, as measured by the oxalic acid-uranyl sulphate method of Anderson and Robinson,[7] to about one-third. Using this filter, it was possible to cure infants who had tetany without causing erythema or pigmenta-

7. Anderson, W. T., and Robinson, F. W.: The Oxalic Acid-Uranyl Sulphate Ultraviolet Radiometer, J. Am. Chem. Soc. **47**:718, 1925.

tion of the skin. The intensity of the radiant energy was frequently checked, and the length of exposure varied accordingly. A distance of 40 cm. was used. Serum calcium was determined by the Clark and Collip [8] modification of the method of Kramer and Tisdall.[9] Inorganic phosphate in the serum was estimated by the method of Fiske and Subbarow.[10]

Our results confirm those previously reported. Following exposure to ultraviolet radiant energy, the serum calcium rises regularly to normal. According to Hoag,[3] approximately fourteen days are required to bring about this result.

IRRADIATED CHOLESTEROL

Hess [11] and Rosenheim and Webster [12] have shown that cholesterol, exposed to ultraviolet radiant energy, is effective in the prevention and treatment of rickets in animals. Hess was also able to cure rickets in infants with irradiated cholesterol.[13] His observations have been unanimously confirmed by numerous observers.[14] Similar results have been obtained by feeding various irradiated vegetable oils and foods.[15]

There have been several reports on the results of treatment of infants with tetany by means of irradiated foodstuffs. György [16] reported favorable results following the feeding of irradiated dry milk to nine infants with tetany and rickets. The serum calcium rose to normal in from twenty-two to forty-five days. McKay and Shaw [17] used irradiated dry milk successfully in one infant with tetany.

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8. Clark, E. P., and Collip, J. B.: Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

9. Kramer, B., and Tisdall, F. F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475 (Aug.) 1921.

10. Fiske, C. H., and Subbarow, Y.: The Colorimeter Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

11. Hess, A. F.; Weinstock, M., and Helman, F. D.: Antirachitic Value of Irradiated Phytosterol and Cholesterol, J. Biol. Chem. **63**:305 (March) 1925.

12. Rosenheim, O., and Webster, T. A.: The Antirachitic Properties of Irradiated Sterols, Biochem. J. **20**:537, 1926.

13. Hess, A. F.: Antirachitic Activity of Irradiated Cholesterol, Ergosterol and Allied Substances, J. A. M. A. **89**:337 (July 30) 1927.

14. György, P.; Jenke, M., and Popoviciu, G.: Jahrb. f. Kinderh. **112**:35 (March) 1926. György, P.: Klin. Wchnschr. **4**:1118, 1925. Goetche, O., and Tolnai, M.: Jahrb. f. Kinderh. **114**:199, 1926. Hottinger, A.: Bestrahltes Cholesterin in der Therapie der Rachitis, Klin. Wchnschr. **5**:2061 (Oct.) 1926.

15. György, P.: "Jekorisierte" Milch in der Therapie der Rachitis, Jahrb. f. Kinderh. **111**:201, 1926. McKay, H. M. M., and Shaw, H. F.: Irradiation of Foodstuffs with Ultraviolet Light, Lancet **1**:8 (Jan. 2) 1926. Kramer, B.: Rickets in Infants: Treatment with Irradiated Milk, Am. J. Dis. Child. **30**:195 (Aug.) 1925.

16. György (footnote 15, first reference).

17. McKay and Shaw (footnote 15, second reference).

There are few reports on the effects of irradiated cholesterol on the serum calcium of infants with tetany. Parsons [18] reported a rise in the serum calcium of from 7.15 to 10.4 mg. per hundred cubic centimeters after sixty days of treatment, in a child, aged 3 years, with severe rickets. The tetanic symptoms are not mentioned. Until a month before cholesterol was given, this patient had received cod liver oil for a period of five months.

Vollmer [19] fed irradiated cholesterol incorporated in zwiebach to two infants with manifest tetany. The symptoms disappeared promptly, simultaneous with the healing of the associated rickets. Calcium deter-

TABLE 2.—*The Effect of Irradiated Cholesterol on the Serum Calcium and Inorganic Phosphate of Five Infants with Tetany*

Patient	Color	Sex*	Age	Weight, Kg.	Date	Length of Treatment Days	Serum Calcium Mg. per Cent	Inorganic Phosphorus Mg. per Cent	Comment
11 A. W.	black	♀	27 mos.	6.8	4/14/27	0	6.7	2.9	Laryngismus stridulus
					4/26/27	12	7.5	4.1	Developed pneumonia
					5/ 3/27	19	9.5	2.0	
12 V. B.	white	♀	14 mos.	8.4	4/ 9/27	0	6.3	3.0	Anodal reversal C.O.C.†
					4/15/27	6	7.7	...	
					4/19/27	10	8.0	4.4	>5; laryngismus stridulus
					4/26/27	17	7.9	4.7	E. R. normal
13 W. S.	black	♂	18 mos.	9.5	4/11/28	0	4.6	2.9	Convulsions;
					4/16/28	5	6.8	3.9	anodal reversal C.O.C. 2.8;
					4/21/28	10	7.7	4.7	2 Gm. cholesterol daily
					4/27/28	16	9.2	5.3	
					5/ 1/28	20	10.2	4.7	
14 C. C.	white	♂	6 mos.	6.4	4/13/28	0	7.2	4.7	Anodal reversal C.O.C. 4.5
					4/19/28	6	8.6	5.3	
15 A. K.	black	♂	15 mos.	8.2	4/12/28	0	8.3	3.1	Anodal reversal; had received cod liver oil for a long time before admission
					4/19/28	7	8.3	3.5	
					4/21/28	9	7.3	3.2	

* In this column ♂ indicates male; ♀, female.
† C.O.C. indicates cathodal opening contraction.

minations before and after treatment are not reported. Hottinger [20] also reported the cure of tetany in infants with irradiated cholesterol, but does not give any clinical details or figures for serum calcium.

In table 2 are shown the results following the administration of irradiated cholesterol to four infants with tetany and to a fifth with a moderate degree of hypocalcemia. Chemically pure cholesterol (Eimer

18. Parsons, L. G.: The Value of Irradiated Cholesterol in the Treatment of Rickets, Brit. M. J. **1**:519, 1926.

19. Vollmer, H.: Zur Cholesterin Therapie der Rachitis, Ztschr. f. Kinderh. **44**:87, 1927.

20. Hottinger (footnote 14, fourth reference).

and Amend) was irradiated with a mercury vapor arc in quartz at 30 cm. for thirty minutes. One gram, freshly irradiated, was given daily with cereal. Patient W. S. (case 13) received 2 Gm. daily. In two of the five patients the serum calcium rose to normal in sixteen and nineteen days, respectively. In patient V. B. (case 12) the serum calcium rose from 6.3 to 7.9 mg. per hundred cubic centimeters after seventeen days of treatment; and in patient A. K. (case 15) the serum calcium fell from 8.3 to 7.3 mg. per hundred cubic centimeters after nine days of therapy. In patient C. C. (case 14), who received treatment for six days only, the serum calcium rose from 7.2 to 8.6 mg. per hundred cubic centimeters. On the whole, the cure of tetany in infants with irradiated cholesterol in doses of 1 Gm. daily is slower and less constant than after the administration of ultraviolet radiant energy or irradiated ergosterol.

IRRADIATED ERGOSTEROL

Hess and Windaus [21] have recently shown that it is probably not cholesterol itself, but some contaminating sterol or sterols intimately associated with it that is responsible for the antirachitic effect of irradiated cholesterol. These investigators found that ergosterol which has been exposed to ultraviolet radiant energy is effective in the prevention and treatment of rickets in animals, a daily dose of 0.001 mg. being sufficient to prevent or cure rickets in a rat. Rosenheim and Webster [12] had noted earlier the marked antirachitic effect of irradiated ergosterol. As approximately 1 mg. of irradiated cholesterol or 20 mg. of cod liver oil is required to protect a rat from rickets,[13] it is apparent that irradiated ergosterol is about 1,000 times more potent as an antirachitic agent than irradiated cholesterol, and 20,000 times more potent than cod liver oil.

The clinical efficacy of irradiated ergosterol in the treatment of infants with rickets and tetany has been reported by several observers.[22] Beumer and Falkenheim [23] gave from 2 to 3 mg. of irradiated ergosterol daily to five infants with rickets and varying degrees of hypocalcemia. In three of the five patients, the serum calcium rose to normal levels within from ten to twenty days; in the remaining two patients, it rose

21. Hess, A. F., and Windaus, H.: Contaminating Substances as Factors in Activation of Cholesterol by Irradiation, Proc. Soc. Exper. Biol. & Med. **24**:369 (Jan.) 1927; Development of Marked Activity in Ergosterol Following Ultraviolet Irradiation, ibid. **24**:261 (Feb.) 1927.

22. Beumer, H., and Falkenheim, C.: Ueber das Ergosterin und seine antirachitische Wirksamkeit bei Säuglingen, Klin. Wchnschr. **6**:798, 1927. György, P.: Therapeutische Versuche mit bestrahltem Ergosterin, Klin. Wchnschr. **6**:580, 1927. Prinke, G.: Klinische Erfahrungen mit dem neuen Rachitisheilmittel von Windaus-Hess, Klin. Wchnschr. **6**:1644 (Aug. 27) 1927. Karelitz, S.: Treatment of Rickets with Irradiated Ergosterol (Vigantol), Proc. Soc. Exper. Biol. & Med. **25**:576 (April) 1928.

23. Beumer and Falkenheim (footnote 22, first reference).

gradually but was still below 9 mg. per hundred cubic centimeters thirty days after treatment had been begun.

György [24] gave irradiated ergosterol in doses of from 2 to 4 mg. daily to fourteen infants, seven of whom had tetany, either latent or manifest, and seven others hypocalcemia of moderate degree. In all fourteen patients the serum calcium values rose to normal limits within from twenty-three to thirty-three days. In one patient the serum calcium value rose from 8 to 10.1 mg. per hundred cubic centimeters in fourteen days.

In the present study fifteen infants with hypocalcemia of varying degrees were treated with irradiated ergosterol and the effect on the clinical manifestations and the calcium concentration of the serum was studied. The inorganic phosphate content of the serum was also determined before and after treatment was started. Four milligrams of irradiated ergosterol in 1 per cent suspension in sesame oil was given daily. In all but three infants (serum calcium values 8.6, 8.7 and 8.8 mg. per hundred cubic centimeters, respectively) evidences of mechanical or electrical hyperirritability were present. In eight of the fifteen patients, the serum calcium values before treatment were 7.5 mg. per hundred cubic centimeters or lower.

Following the administration of irradiated ergosterol there was a prompt disappearance of the symptoms of active tetany. In only one patient were convulsions noted after the first day of treatment. The electrical reactions returned to normal when the serum calcium reached about 8.5 mg. per cent, as is usual in infants with tetany following other methods of treatment. There was no striking effect on the general condition.

Serum Calcium.—The effect of irradiated ergosterol on the serum calcium is shown in table 3. In every instance the serum calcium rose with striking rapidity. In twelve of the fifteen infants the serum calcium reached a normal level in from three to twelve days. For patients in whom the initial serum calcium values were 7.5 mg. per hundred cubic centimeters or below the time required was six, seven, seven, seven, seven, eight, ten and twelve days, respectively. In one instance the calcium rose to 10.2 mg. per hundred cubic centimeters after seven days of treatment and subsequently fell to 9.2 mg., still remaining, however, within the normal limits. In one patient on whom observations were made after the discontinuation of treatment, the serum calcium remained constant at 10 mg. per hundred cubic centimeters for nineteen days at which time the infant left the hospital. In three patients the serum calcium remained below 9 mg. per hundred cubic centimeters after treatment. Two of these left the hospital on the

24. György (footnote 22, second reference).

TABLE 3.—*The Effect of Irradiated Ergosterol on the Serum Calcium and Inorganic Phosphate of Fifteen Infants with Hypocalcemia*

Patient	Color	Sex*	Age	Weight, Kg.	Date, 1928	Length of Treatment Days	Serum Calcium Mg. per Cent	Inorganic Phosphorus Mg. per Cent	Comment
21 F. T.	white	♂	5 mos.	5.7	3/13	0	7.5	...	Pneumonia;
					3/17	4	6.0	3.1	anodal reversal C. O. C. 3.6
					3/23	10	10.1	...	
					3/27	14	10.7	6.3	E. R. normal
22 D. R.	black	♂	5 mos.	6.6	3/15	0	6.5	3.1	Pneumonia;
					3/21	5	8.0	1.5	convulsions;
					3/23	7	9.2	1.6	anodal reversal
					3/27	11	9.6	2.5	E. R. normal
23 N. E.	white	♂	14 mos.	7.8	3/17	0	7.3	3.8	Convulsions;
					3/23	4	8.6	6.2	E. R. normal
									E. R. normal
24 G. B.	black	♀	2 mos.	4	3/22	0	8.6	3.9	Gastro - enteritis
					3/29	5	10.9	6.7	
25 C. C.	black	♂	5 mos.	4.7	3/ 2	0	4.8	5.4	Anodal reversal
					3/ 6	4	8.0	7.0	
					3/ 9	7	9.1	6.6	Anodal reversal
					3/13	11	10.1	6.3	
26 J. C.	white	♀	11 mos.	9	3/13	0	5.9	3.1	Anodal reversal; C. O. C. 4.3
					3/17	4	8.6	...	E. R. normal
					3/29	16	8.7	4.3	
27 J. D.	white	♂	3 mos.	5	3/ 1	0	8.8	2.2	Congenital syphilis
					3/ 3	0	...	...	Treatment started
					3/ 6	3	10.1	3.4	E. R. normal
28 M. O.	black	♂	11 mos.	7.3	3/ 2	0	8.7	2.9	
					3/ 6	4	8.7	...	E. R. normal
					3/ 9	7	10.2	2.2	
					3/13	11	9.2	3.6	
29 J. S.	white	♂	5 mos.	5.7	4/19	0	5.7	2.2	Convulsions;
					4/26	7	8.2	3.5	erysipelas;
					5/ 1	12	9.9	4.7	anodal reversal C. O. C. 4.8; 3 Gm. calcium chloride at hourly intervals on 4/19
30 A. M.	white	♂	11 mos.	10	3/ 5	0	5.6	...	Convulsions; crow; 3 Gm. calcium chloride at 4 hourly intervals
					3/ 6	1	...	...	E. R. normal
					3/11	6	9.5	7.1	
31 M. H.	white	♀	8 mos.	7.7	3/11	0	5.1	...	Convulsions;
					3/14	3	6.0	4.3	anodal reversal C. O. C. 4.2; 4 Gm. calcium chloride; anodal reversal
					3/19	8	9.7	5.0	
32 A. C.	white	♀	11 mos.	8.6	2/29	0	7.3	1.0	Pneumonia; anodal reversal
					3/ 5	5	9.5	3.6	E. R. normal
					3/ 8	8	9.4	4.7	
33 A. G.	black	♂	12 mos.	5.2	3/13	0	7.1	2.8	
					3/17	4	8.5	4.0	
34 M. J.	black	♀	5 mos.	5.7	2/23	0	6.7	8.2	Crow; nystagmus
					3/ 1	7	10.4	8.6	E. R. normal
					3/ 5	11	7.3	8.2	E. R. normal
					3/10	16	...	...	Ergosterol discontinued
					3/13	..	10.6	6.3	3 days after treatment discontinued
					3/29	..	10.6	6.6	19 days after treatment discontinued
35 E. V.	black	♀	6 wks.	3.5	6/22	0	7.3	5.1	Convulsions
					6/29	7	10.5	6.5	

* In this column ♂ indicates male; ♀, female.

fourth day of treatment (cases 23 and 34). In the third patient (case 26) the serum calcium rose from 5.9 to 8.7 mg. per hundred cubic centimeters on the sixteenth day, at which time treatment was discontinued.

Inorganic Phosphate.—The effect of irradiated ergosterol on the serum inorganic phosphate is also shown in table 3. As one might expect from the variability in the values of inorganic phosphate in patients with infantile tetany, the influence of irradiated ergosterol is less constant than in the case of the serum calcium; however, the lower values rise after treatment as they do following exposure to ultraviolet radiant energy. On the whole, the effect of irradiated ergosterol on the serum calcium and inorganic phosphate is similar to that of ultraviolet radiant energy, but more rapid.

COD LIVER OIL

Though cod liver oil is widely used in the treatment of infants with tetany, published studies on its effect on the serum calcium in this condition are meager, the remarks of Hoag [3] being the only ones in the literature which treat the subject directly. In Hoag's patient A. G., previously treated with calcium chloride, the serum calcium rose from 7.1 to 8.8 mg. per hundred cubic centimeters in twenty-six days. On the thirtieth day it was still 8.7 mg. On the fifty-third day the serum calcium was 9.4 mg. per hundred cubic centimeters. In patient D. G. the serum calcium rose only from 5.4 to 6.2 mg. per hundred cubic centimeters in twenty days, at which time symptoms were still present (crow, anodal reversal). In Hoag's third patient the serum calcium remained unchanged after fourteen days of treatment at 8.4 mg. per hundred cubic centimeters. Hoag gave 4 cc. of cod liver oil daily.

In two rachitic infants treated by Howland and Kramer [25] with cod liver oil, the serum calcium values of 8.7 and 8.8 mg. per hundred cubic centimeters remained unchanged after treatment for sixty-three and thirty-nine days, respectively, although during the time the inorganic phosphate rose steadily. They gave 6 and 12 cc., respectively, of cod liver oil daily.

Rosenstern [26] studied the effect of cod liver oil in large doses (25 cc. daily) on the clinical manifestations and electrical reactions (cathodal opening contraction) of twenty-two infants with tetany. He found that in eighteen the reaction to the cathodal opening current [27]

25. Howland, J., and Kramer, B.: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

26. Rosenstern, I.: Zur Wirkung des Lebertrans auf Rachitis und spasmophile Diathese, Berl. klin. Wchnschr. **47**:822 (May) 1910.

27. A normal reaction to a cathodal opening current is often obtained with serum calcium values of 7 mg. per hundred cubic centimeters or even lower.

returned to normal within three weeks; in two infants the electrical hyperirritability was decreased but still remained abnormal, while in two others there was no effect. Symptoms (convulsions, crow) usually disappeared by the end of the first week, but the facial sign persisted, at times for two months after treatment had been started. Similar

TABLE 4.—*The Effect of 12 Cc. of Cod Liver Oil Daily on the Serum Calcium and Inorganic Phosphate of Ten Infants with Rickets and Tetany*

Patient	Color	Sex	Age	Weight, Kg.	Date	Length of Treatment Days	Serum Calcium Mg. per Cent	Inorganic Phosphorus Mg. per Cent	Comment
41 M. M.	white	♀	17 mos.	7.3	1/14/27	0	7.0	3.1	Convulsions
					1/26/27	12	8.5	3.7	
42 S. S.	white	♀	17 mos.	11.1	4/ 5/26	0	4.3	...	Crow; carpopedal spasm
					4/14/26	9	6.1	...	Carpopedal spasm gone,
					4/21/26	16	5.7	...	Crow persists
43 S. H.	black	♀	16 mos.	6.3	2/15/26	0	7.4	...	Nystagmus;
					2/20/26	5	7.0	...	anodal reversal
44 L. G.	white	♂	3 mos.	4.6	2/13/26	0	7.6	...	Convulsions
					2/20/26	7	6.6	...	Carpopedal spasm
45 A. D.	black	♂	4 mos.	5.6	3/16/26	5	8.1	...	Anodal reversal
					3/23/26	12	8.8	...	
46 H. L.	black	♂	4 mos.	5.1	3/27/26	0	7.4	...	Convulsion
					4/ 7/26	11	7.5	...	9 days after treatment; pneumonia past 4 days
47 A. G.	black	♂	14 mos.	8.8	12/18/26	0	6.7	3.6	Convulsions
					12/30/26	13	8.6	3.7	No symptoms
48 B. F.	white	♀	22 mos.	9	11/16/26	0	7.1	3.4	Convulsions
					11/23/26	6	7.5	4.1	Carpopedal
					11/28/26	12	7.1	...	spasm
49 B. F.	white	♀	13 mos.	....	2/13/26	0	7.7	...	Carpopedal
					2/20/26	7	5.8	...	spasm
50 G. S.	white	♂	2¼ mos.	....	4/ 5/26	0	7.0	...	Serum calcium
					4/15/26	10	6.3	...	was 7.3 mg.
					4/26/26	21	6.7	5.2	per cent 6 weeks before treatment
					5/ 5/26	30	6.3	...	
					5/14/26	39	6.0	6.1	Anodal reversal
					5/21/26	46	6.8	...	5/18 had been irradiated one day

* In this column ♂ indicates male; ♀, female.

results were obtained when smaller amounts of cod liver oil containing phosphorus were given.

Brown and his co-workers[28] reported favorable results in five infants with tetany following the daily administration of 2 cc. of cod liver oil.

28. Brown, A.; MacLachlan, I. F., and Simpson, R.: Cod Liver Oil Without Phosphorus as Effective as Cod Liver Oil with Phosphorus in Rickets or Tetany, Canad. M. A. J. **11**:552, 1921.

Results following the administration of cod liver oil to ten infants with tetany are shown in table 4. Twelve cubic centimeters of cod liver oil of reputed high potency was given daily in three doses. Precautions were taken that the infant received the complete amount.

In three patients in whom serum calcium determinations were made within seven days after treatment was started, the serum calcium fell (cases 43, 44, 49). In one patient this amounted to only 0.4 mg. per hundred cubic centimeters, but in the other two (cases 44 and 49) the decrease amounted to 1 and 1.9 mg. per hundred cubic centimeters, respectively. There was, however, no exaggeration of the clinical manifestations. In case 42, the serum calcium sixteen days after treatment had been instituted was still 5.7 mg. per hundred cubic centimeters. In no case did the serum calcium reach normal limits. In case 46, convulsions occurred nine days after treatment had been begun. In patient G. S. (case 50), the serum calcium fell steadily from 7 to 6 for thirty-nine days after treatment was started. On the thirty-ninth day there was still anodal reversal. On the forty-sixth day, the serum calcium was 6.8 mg. per hundred cubic centimeters, the child having received one treatment with ultraviolet radiant energy in the meantime. It is of additional interest that this patient received whole lactic milk during the entire period of his treatment and for six weeks previously.

On the whole, it appears that cod liver oil is unreliable as a therapeutic agent in tetany. From the published data [26] it seems that, when given in large amounts and over a long period of time, cod liver oil may be curative in a large percentage of cases. For clinical purposes, however, since surer and quicker means are at hand, it should not be relied on in the treatment of a condition potentially so dangerous as tetany. Furthermore, data already given indicate that it may aggravate the condition and that it may be dangerous in severely ill patients.[29]

The effect of cod liver oil and of ultraviolet radiant energy on the clinical manifestations of rickets appears to be identical. Deposition of calcium in the bones and increase in the serum phosphate occur about

29. Huldschinsky (Ztschr. f. Kinderh. **26**:207, 1920) states that an exaggeration of the symptoms of tetany may occur immediately following treatment with ultraviolet radiant energy. He therefore advises against its uses in patients with manifest tetany until other treatment has first been given. He attributes the exaggeration in symptoms to the rapid deposition of calcium in the bones, thus causing a temporary lowering of the calcium concentration in the serum. It is conceivable that a fall in the serum calcium and an exaggeration of tetanic symptoms may occur after any therapeutic agent which cures rickets. From a theoretical point of view, however, cod liver oil should still be the most dangerous, since it is, in comparison with other substances of its class, much less active in raising the serum calcium than in promoting calcification.

as rapidly after one form of therapy as after the other. The difference in the response of the infant with tetany, a closely associated condition, is therefore of great interest.

THE EFFECT OF COD LIVER OIL AND IRRADIATED ERGOSTEROL ON THE SERUM CALCIUM OF INFANTS WITH TETANY

The effect of cod liver oil and irradiated ergosterol on infants with tetany is shown in table 5. The effect on the serum calcium was as rapid, if not more rapid, than when irradiated ergosterol was given alone. In the four infants with active tetany, the serum calcium rose

TABLE 5.—*The Effect of 4 Mg. of Irradiated Ergosterol and 24 Cc. of Cod Liver Oil Daily on the Serum Calcium and Inorganic Phosphate of Five Infants with Tetany*

Patient	Color	Sex*	Age	Weight, Kg.	Date, 1928	Length of Treatment Days	Serum Calcium Mg. per Cent	Inorganic Phosphorus Mg. per Cent	Comment
51 T. M.	white	♂	7 mos.	4.4	4/30	0	7.1	4.2	Convulsions;
					5/ 4	4	10.8	4.6	anodal reversal
52 J. A.	white	♂	7 mos.	7.4	5/ 1	0	7.1	1.7	Convulsions; anodal reversal
					5/ 5	4	9.3	1.9	Desperately ill pneumonia
53 P. B.	white	♂	8 mos.	10	5/18	0	6.1	4.0	Convulsions;
					5/22	4	7.7	3.9	1 Gm. calcium
					5/27	9	9.4	4.2	lactate twice
54 M. D.	white	♂	6 mos.	6.1	5/11	0	6.5	4.3	Marked laryngismus stridulus; anodal reversal
					5/14	3	7.2	...	Cod liver oil
					5/18	7	10.2	5.7	discontinued
55 A. G.	black	♀	10 mos.	5.7	6/22	0	8.3	3.2	
					6/29	7	10.0	3.8	

* In this column ♂ indicates male; ♀, female.

to normal in four, four, seven and nine days, respectively. The large doses of cod liver oil seemed to reinforce the action of the irradiated ergosterol.

COMMENT

Of the group of substances which exert a lasting effect on the serum calcium of infants with tetany, irradiated ergosterol appears to be the most rapid in its action. In the twenty patients so treated (including those who received cod liver oil) the serum calcium rose to a normal level within from three to twelve days, except in one patient. The usual time was seven days. In our series the daily dosage was 4 mg. Whether a more rapid effect could be produced by giving larger amounts was not ascertained.

The rise in the serum calcium was as constant as and more rapid than that following treatment with ultraviolet radiant energy which ordinarily requires about fourteen days for cure. With irradiated cholesterol, the effect is still slower and less constant. For clinical purposes, cod liver oil cannot be relied on to raise the serum calcium. Whether it is adequate to protect the infant against the development of tetany is questionable.

The treatment of choice in infants with active tetany appears to be a combination of calcium chloride (which causes an immediate but transient rise in the serum calcium) in large doses (1 Gm. every one to two hours during the first few hours) in conjunction with irradiated ergosterol.

SUMMARY

1. Of the group of agents which exert a lasting effect on the clinical manifestations and the serum calcium of infants with tetany, irradiated ergosterol is the most rapid in its effect.

2. In a series of twenty infants so treated (4 mg. of irradiated ergosterol daily), the clinical symptoms disappeared promptly, and the serum calcium rose to normal on the average in seven days. This is more rapid than cure following ultraviolet radiant energy (fourteen days).

3. Clinical improvement and a rise in the serum calcium are slower and less constant after treatment with irradiated cholesterol than after the administration of either irradiated ergosterol or ultraviolet radiant energy.

4. Cod liver oil is inadequate in the treatment of tetany in infants, its action being too slow and too inconstant.

5. When cod liver oil and irradiated ergosterol are given together, the curative effect is as rapid as when irradiated ergosterol is given alone.

6. The treatment of choice for infants with tetany appears to be a combination of calcium chloride, which has a marked immediate effect on the serum calcium and irradiated ergosterol.

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CHEMICAL CHANGES OCCURRING IN THE BODY AS A RESULT OF CERTAIN DISEASES

IV. PRIMARY PNEUMONIA IN CHILDREN *

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For a number of years there has been a good deal of interest in the retention of chloride during pneumonia and in the low concentration of chloride in the blood. In 1869, Leyden [1] concluded that the tissues must contain more water during fever than normally, and this has been confirmed by later analyses of the tissues themselves. Hutchinson [2] reviewed the earlier work on chloride metabolism during pneumonia and showed that in adults about 2 Gm. of sodium chloride a day may be retained during the fastigium, and that this is released from one to two days after the crisis. He showed that the pneumonic exudate could account for only from 5 to 7 Gm. of sodium chloride, which is about only one-half the amount retained.

Peabody [3] confirmed the low concentration of chloride in the blood and showed that it was concomitant with retention of chloride. He was unable to find a depot for the storage of chloride and concluded that it must be stored diffusely throughout the body. He also found a slightly low plasma bicarbonate content. Barach, Means and Woodwell [4] showed that the carbon dioxide absorption curve is at a lower level than normal and rises again after the crisis. Hastings, Neill, Morgan and Binger,[5] and Binger, Hastings and Sendroy [6] determined the p_H of the serum and corrected previous calculations which had indicated a slight acidosis.

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* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

1. Leyden, E.: Untersuchungen über das Fieber, Deutsches Arch. f. klin. Med. **5**:273, 1869.

2. Hutchinson, R.: Chloride Metabolism in Pneumonia and Acute Fevers, J. Path. & Bact. **5**:406, 1898.

3. Peabody, F. W.: Studies of the Inorganic Metabolism in Pneumonia with Especial Reference to Calcium and Magnesium, J. Exper. Med. **17**:71, 1913; The Bicarbonate Content of the Blood in Pneumonia, ibid. **16**:701, 1912.

4. Barach, A. L.; Means, J. F., and Woodwell, M. N.: The Hydrogen Ion Concentration and Bicarbonate Level in Pneumonia, J. Biol. Chem. **50**:413, 1922.

5. Hastings, A. B.; Neill, J. M.; Morgan, H. J., and Binger, C. A. L.: Blood Reaction and Blood Gases in Pneumonia, J. Clin. Investigation **1**:25, 1921.

6. Binger, C. A. L.; Hastings, A. B., and Sendroy, J.: A Further Study of Blood Reaction and Blood Gases in Pneumonia, J. Exper. Med. **45**:1081, 1927.

Buckman, Adams, Smith and Edwards [7] confirmed the lowering of the level of the carbon dioxide absorption curve and pointed out that, if the hydrogen ion concentration is corrected for the increased dissociation of water at higher temperatures, the blood in pneumonia becomes somewhat more alkaline in the sense of a decrease in the ratio of the hydrogen ion concentration to the hydrogen ion concentration of water at neutrality. They bring out that the venous and arterial bicarbonate are lower than normal and that the arterial oxygen saturation is below the normal, but the venous saturation may be higher than normal. Since both the venous and arterial bicarbonate and oxygen contents approach each other in value, they would explain this as being brought about by more rapid circulation.

Suderman, Austin and Camac [8] reviewed the recent chemical studies of the blood pneumonia and determined the chloride, bicarbonate, total base, freezing point, conductivity, protein and urea concentration of the serum of pneumonia patients before and after the crisis. This work brought out that the freezing point, conductivity and total base are lowered in amounts roughly proportional to the lowering of the chloride ion concentration. From the change in protein concentration, they thought dilution of the blood likely. Soule, Buckman and Darrow [9] reported the results on the determinations of blood volume together with chloride concentrations. They found an increase in the plasma volume and showed that the increase in the plasma volume together with a tendency to an increase in the water content of the body was sufficient to explain not only the low concentration of the blood chloride, but also the storage of chloride in the body during the fever.

Thus it would seem, from previous studies, that the chemical composition of the blood in pneumonia is characterized by low chloride, normal or slightly diminished bicarbonate, low freezing point depression, low total base and high normal p_H.

In previous studies [10] from this laboratory, it has been shown that the osmotic pressure of the blood tends to be maintained at a fairly

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7. Buckman, T. E.; Adams, F. D.; Smith, M., and Edwards, H. T.: Chemical Studies of the Blood in Pneumonia, Boston M. & S. J. **193**:997, 1925.

8. Suderman, F. W.; Austin, J. H., and Camac, J. G.: Studies in Serum Electrolytes in Lobar Pneumonia, J. Clin. Investigation **3**:37, 1926.

9. Soule, H. C.; Buckman, T. E., and Darrow, D. C.: Blood Volume in Fever, J. Clin. Investigation **5**:229, 1928.

10. Hartmann, A. F.: The Chemical Changes Occurring as the Result of Certain Diseases: I. The Effects of Diarrhea, Vomiting, Dehydration and Oliguria on the Acid-base Balance of the Plasma of Infants with Mastoiditis, Am. J. Dis. Child. **35**:557 (April) 1928. Hartmann, A. F., and Darrow, D. C.: Acute Hemorrhagic Nephritis, Subacute Nephritis, Chronic Nephritis, II., J. Clin. Investigation **6**:127, 1928; The Composition of the Plasma in Severe Diabetic Acidosis, and the Changes Taking Place During Recovery, III., ibid., to be published.

constant level despite great changes in the concentration of individual constituents. It has been found that the chief factors which affect the chemical balance of the blood are loss of electrolyte by vomiting or diarrhea, disturbances in acid-base excretion by the kidney, appearance of large amounts of acids or salts in the blood (ketosis and salt fever) and disturbances leading to edema or dehydration. The present work was undertaken to study much the same factors as did Suderman, Austin and Camac.[8] It confirms their work, but points out certain differences which are probably characteristic of children with pneumonia. Furthermore, it will be pointed out that the chief chemical changes in the blood in pneumonia may be explained by the known increase in the plasma volume and the known tendency to retention of water during fever.

The determinations indicated in the table were all made on venous blood collected under oil with as little stasis as possible; in all but the first three the blood was taken from the external jugular vein. Serum was used except for some estimations on the lactic acid, sugar and non-protein nitrogen. The methods and calculations are given in a previous publication.[11]

It was shown that the undetermined acids in normal subjects are about 5 ± 5 milli-equivalents; that the osmolar concentration of the total electrolytes is 277 ± 12 millimols (mM.); that the osmolar concentration of the total electrolytes, sugar and urea is 290 ± 20 millimols, and that the osmolar concentration of the serum indicated by the freezing point is 314 ± 15 millimols. The osmolar concentration not accounted for averaged 8 per cent and reached a maximum of 11.5 per cent in normal subjects. This corresponds to an undetermined fraction of about 20 millimols.

The significance of the columns in table 1 is fairly obvious. The "day from the crisis" denotes the day before the crisis (indicated with a minus sign) or the day after the crisis (indicated with a plus sign), the day of the crisis being the zero day. The ratio $\frac{\text{"A"}}{\text{B}}$ represents in per cent the proportion of the freezing point accounted for by the various chemical determinations. A part of the filtrate prepared for the estimation of lactic acid was distilled into Scott-Wilson reagent. In no instance were appreciable amounts of acetone detected in this way.

The data indicate fairly well the chemical composition of the serum in pneumonia. It should be noticed that the chief changes in the chemical composition of the blood concern the electrolyte. Thus the total base concentration is reduced as well as the chloride and bicarbonate concentration. This gives a low total electrolyte concentration, and since there

11. Darrow, D. C., and Hartmann, A. F.: A Comparison of the Calculated and Determined Osmolar Concentration of Normal Serum, Am. J. Dis. Child., in press.

TABLE 1.—*Acid-Base and Osmolar Concentration of Venous Serum*

								Acid-Base Concentration by Volume							Osmolar Concentration					
Case	Date	Age, Years	Weight, Kg.	Day of Disease	Day from Crisis; Crisis = 0 Day	Temperature, C.	p_H	BCl, M-eq.	$BHCO_3$, M-eq.	B—Protein, M-eq.	B_2HPO_4 + BH_2PO_4, M-eq.	B—Lactate, M-eq.	Total Acid, M-eq.	Total Base, M-eq.	Dextrose, Millimols	Urea, Millimols	Total Electrolyte, Millimols	Total Calculated (A) Millimols	Freezing Point (B) Millimols	A / B per Cent
1	2/14/27	3.5	14.90	5	−3	40.5	7.49	91	18.7	16.0	(2)	1.7*	**129**	**134**	(6)	8.9*	246	**261**	...	..
1	2/19/27	3.5	15.00	11	+2	37.5	7.41	89	23.1	17.0	1.9	1.7*	**133**	**141**	5.4*	7.5*	254	**267**	...	..
2	2/21/27	7.5	23.30	7	−2	40.5	7.49	100	22.9	14.1	(2)	1.1*	**140**	...	(6)	10.4*	268	**284**	...	..
2	2/25/27	7.5	22.25	11	+2	37.5	7.50	97	25.4	17.0	(2)	1.0*	**142**	**147**	(6)	8.9*	276	**291**	...	..
3	2/21/27	3	12.95	5	−4	40.5	7.41	101	20.0	15.3	(2)	2.3*	**141**	**145**	(6)	12.5*	268	**287**	...	..
3†	3/ 1/27	3	12.30	13	+4	38.0	7.47	102	24.8	15.9	(2)	1.7*	**146**	**144**	(6)	9.2*	281	**296**	...	..
4	1/ 6/28	3	10.80	5	**−6 ?**	**40.0**	**7.45**	94	15.6	15.2	1.7	3.5	**130**	...	(6)	7.2	250	**263**	**280**	**95**
4†	1/10/28	3	11.1	9	−2 ?	39.0	7.47	92	22.8	13.1	1.7	4.7	**134**	...	5.7	5.5	256	**267**	**296**	**91**
5	12/21/27	3.5	16.60	5	−1	**41.0**	**7.46**	92	23.5	13.6	1.8	3.1	**134**	...	(6)	8.2	256	**270**	**300**	**90**
5	12/27/27	3.5	15.90	11	+4	37.0	7.47	102	24.1	14.5	2.7	2.5	**146**	...	(6)	6.2	282	**294**	**325**	**91**
6	3/ 5/28	7	21.60	4	−3	40.5	7.43	95	22.1	13.8	2.0	2.7	**138**	**138**	7.6	6.7	259	**273**	**288**	**95**
6	3/ 7/28	7	21.80	6	−1	**40.5**	**7.52**	94	22.7	13.9	1.9	2.8	**135**	**143**	6.9	6.1	232	**275**	**290**	**95**
6	3/13/28	**7**	19.50	12	+4	37.0	**7.46**	104	19.7	18.1	2.1	1.5	**145**	**148**	7.3	6.5	279	**293**	**326**	**90**
7	3/19/28	4	15.60	3	−6	40.5	**7.48**	93	17.1	16.0	2.0	1.9	**130**	**139**	6.3	5.3	248	**260**	**276**	**94**
7	3/28/28	4	15.10	12	+3	37.0	**7.47**	101	24.8	16.8	1.2	2.7	**146**	**150**	6.0	5.6	280	**292**	**324**	**90**
8	4/ 1/28	2	11.40	9	−10	41.0	**7.42**	94	18.3	11.6	1.7	2 2	**128**	**139**	5.5	2.9	243	**251**	**284**	**89**
8	4/24/28	2	10.20	22	+3	37.0	7.44	99	27.8	15.1	2.5	2.4	**147**	**151**	5.3	6.1	278	**290**	**326**	**89**
Average of febrile pneumonia								94.8	19.8	14.4	1.8	2.1	**133**	**140**	...	5.9	255	**270**	**286**	**94**
Average of normal cases								100	24.7	15.2	2.2	2.2	**145**	**151**	6.3	6.9	277	**290**	**319**	**92**

* Determination on oxalated blood. The numbers in the parentheses are assumed values.

† Developed thoracic empyema.

is no compensatory increase in the nonelectrolyte, the depression of the freezing point is less than normal. The proportion of the osmolar concentration both before and after the crisis which could be calculated from the various determinations lies within the range found in normal persons. The slightly better agreement before the crisis in three of five determinations probably is not significant, though this point will be discussed later. The difference between the total acid and the total base concentration is 3 millimols before the crisis and differs so little (— 1 millimols) from that after the crisis that one cannot regard the difference significant. There seems to be a tendency to a slight reduction in the phosphate concentration. In all cases, the lactic acid lies in the normal range of concentration. As stated previously, acetone was not found by collecting the distillate in Scott-Wilson reagent.

Especial attention should be called to the relation of the changes in body weight to the changes in electrolyte concentration. It is well

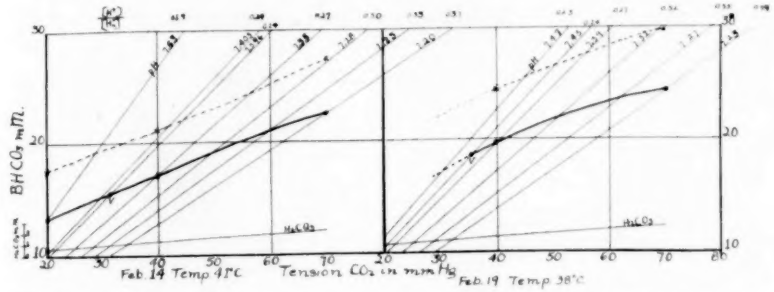

Chart 1.—Carbon dioxide absorption curve during fever and after recovery in case 1.

recognized in pediatric practice that in cases of primary pneumonia the patients tend to show a practically stationary weight during the fastigium. With the crisis there is usually a rather sharp loss in weight. In case 1 this did not occur promptly with the crisis, but neither did the electrolyte concentration increase promptly. In case 2 the patient showed slight loss in weight and little change in the chloride concentration; in case 3, only a slight change in weight and a slight change in electrolyte concentration, and in case 4, a persistent low electrolyte concentration and fairly constant weight. This is apparently because the fever continued on account of the development of empyema. The fluid in the chest might explain the absence of any loss in weight, but the persistent fever probably explains the persistent low electrolyte concentration. The patient in case 5 gained 1.75 Kg. (4 pounds) in weight during the fever and lost 1.5 Kg. (3 pounds) after the crisis, but regained it before the second determination was made. The lowering of the electrolyte concentration is well illustrated in this patient. In case 6 the patient showed

the usual loss in weight with the crisis and lowering of the electrolyte concentration during the fastigium. The patient in case 7 gained 0.8 Kg. (2 pounds) during the fever before the first chemical examination. He did not lose much weight with the crisis but showed the return of the electrolyte to the normal concentration. In case 8 the patient showed a loss in weight and a lowering of the electrolyte concentration. Thus the low electrolyte concentration during the fever is associated with retention of water as indicated by the loss in body weight after the crisis.

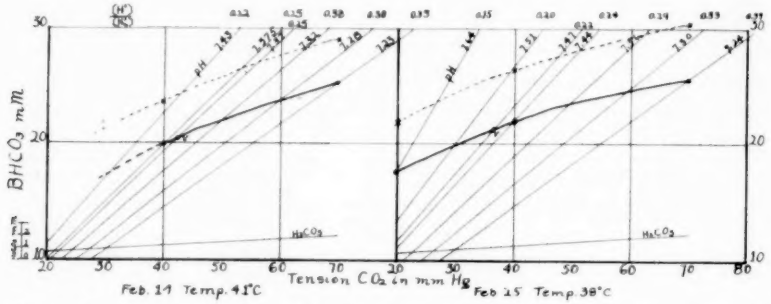

Chart 2.—Carbon dioxide absorption curve during fever and after recovery in case 2.

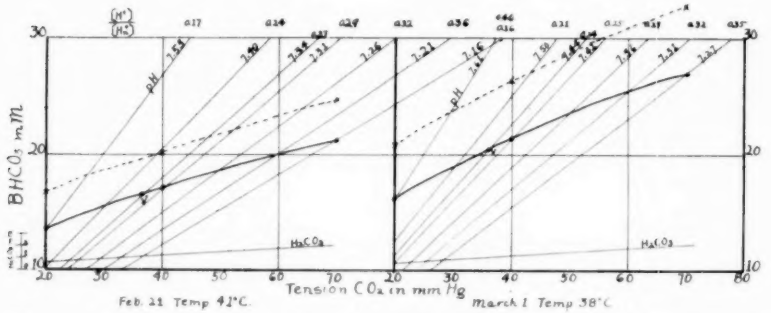

Chart 3.—Carbon dioxide absorption curve during fever and after recovery in case 3.

The colorimetric p_H values were all essentially normal during the fever. There seemed to be a slight tendency to an increase in the p_H, but if the figures were corrected to the temperature of the body (from 40 to 41 C.) they would be from 0.04 to 0.06 lower.

A better idea of the neutrality regulation can be obtained by an examination of the carbon dioxide absorption curves in cases 1, 2 and 3. These curves are of the Haggard-Henderson type. On the ordinates the $BHCO_3$ is expressed in millimols, and on the abscissae, the carbon dioxide tension in millimeters of mercury. The radiating lines denote isohydric conditions. The concentration of hydrogen ions is expressed

as p_H corrected to the temperature noted on the chart and also the acidity ratio. This is the ratio $\left(\frac{H^+}{H^+_n}\right)$ when (H^+) is the hydrogen ion concentration, and (H^+_n) the hydrogen ion concentration of pure water at the temperature noted on the chart. The ratio therefore allows one to compare the deviation from neutrality of the bloods during febrile and afebrile conditions. Chart 4 shows the relation of the acidity ratio to the p_H at 38 and 41 degrees. In making the chart, the p_H at neutrality was taken to be 6.818 at 38 and 6.765 at 41 degrees. In charts 1, 2 and 3 the point V is the venous point on the curve. All curves are corrected to the oxygen saturation of the venous blood and to the temperature noted on the chart. The dotted curve represents approximately the carbon

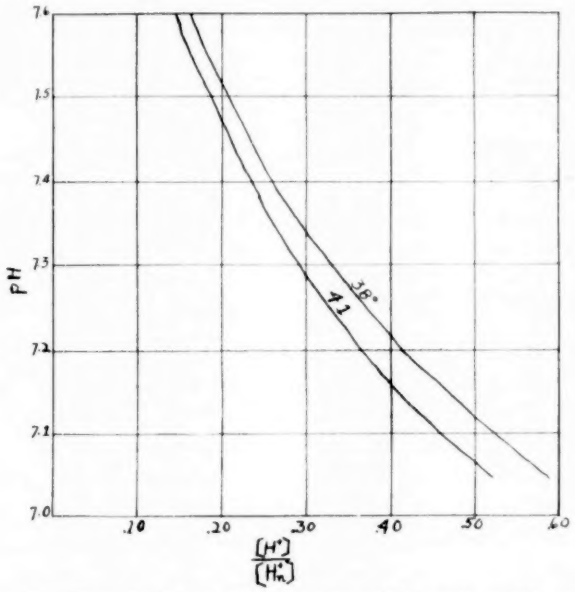

Chart 4.—The relation of the p_H to the acidity ratio at 38 and 40 C.

dioxide curve for true plasma separated at the various tensions. It is calculated from the p_H values of the whole blood curve. The p_H values for the plasma curve may be obtained by finding the p_H of the whole blood curve at the corresponding pressure of carbon dioxide.

METHOD

The curves were derived from oxalated venous blood equilibrated at known tensions of carbon dioxide at 38 C. Carbon dioxide and oxygen were determined in the constant pressure Van Slyke apparatus. The curves were corrected for venous oxygen saturation according to Buckman, Adams, Smith and Edwards.[7] All the febrile curves were corrected to 41 C. according to Stadie and Martin.[12]

12. Stadie, W. C., and Martin, K. A.: Thermo-dynamic Relations of the Oxygen and Base-Combining Properties of Blood, J. Biol. Chem. **60**:191, 1924.

This lowers the level of the carbon dioxide throughout the curve by 4 per cent by volume. These corrections permit the venous point to be measured off on the curves. The p_H was calculated from the well known Henderson-Hanselbach equation.

$$pH = pK_B + \frac{(CO_2) - \alpha_B pCO_2}{\alpha_B pCO_2}$$

$$pK_B = pK_S + (pK_B - pK_S)$$

$$\alpha_B = (1 - 0.0067\ h)\ \alpha_S:$$

pK_S and $pK_B = pK$ of serum and whole blood, respectively. α_B and $\alpha_S = \alpha$ or solubility coefficient of blood and serum, respectively. α_S was chosen at 38 or 41 degrees, as indicated on the charts; $(pK_B - pK_S)$ is the increment which must be given pK_S for various oxygen contents and p_H values; h is the oxygen combining power in per cent by volume, and pCO_2 is the partial pressure of carbon dioxide in millimeters of mercury. The true plasma curve was calculated at the points indicated on the chart by the equation:

$$p_H = 6.10 + \log \frac{(CO_2 - \alpha_S pCO_2)}{\alpha_S pCO_2}$$

The values were taken from the charts in the review by Austin and Cullen.[13] In table 2 the p_H was calculated for venous serum by the Henderson-Hanselbach equation using the pCO_2 found for whole venous blood. The data used are indicated in the charts and in table 2.

An examination of the charts reveals several facts. In each instance, the level of the carbon dioxide curve is lower than normal and lower before than after recovery. In all cases the level of the carbon dioxide curve is lowered by the diminished content of base (table 1), but in cases 1 and 3 this is apparently greater. In all cases, the level of the curve is lowered by the temperature effect, but only in case 2 is this the chief factor. Since serum contains more bicarbonate than erythrocytes, any decrease in the oxygen combining power will increase the level of the whole blood carbon dioxide absorption curve. The magnitude of this effect can be seen from the calculated true plasma curves represented by the dotted line. In cases 2 and 3 the hemoglobin is considerably reduced, probably due to increased plasma volume, and therefore the carbon dioxide curves of the true plasma show an even greater reduction in their level than in that of the whole blood. The carbon dioxide tension is variable and not reliable because of the difficulty of obtaining blood from children who are not crying; however, this error should not be any greater during fever than after recovery, and the charts do not show significant or constant changes in the pressure of carbon dioxide.

13. Austin, J. H., and Cullen, G. E.: Hydrogen Ion Concentration of the Blood in Health and Disease, Medicine **4**:275, 1925.

COMMENT

The p_H values need some explanation. In table 2, the p_H is given as determined colorimetrically, from the carbon dioxide content of whole blood and from the carbon dioxide content of serum. The colorimetric p_H during fever was not corrected for the temperature, but this may be done by substracting 0.06 for each febrile blood. If that is done, there is fair agreement in all three values except in case 2 on February 21 when the colorimetric p_H is apparently too high. The p_H values calculated from the serum carbon dioxide content are subject to fewer errors than the others and are probably the most accurate. There is rather good agreement, however, between the p_H calculated from the whole blood and serum carbon dioxide contents, the greatest divergence being 0.025. It will be noted that in each case the p_H is lower during fever than after

TABLE 2.—*Blood Volume, p_H and Oxygen Saturation*

Case	Date	Temperature, C.	Colorimetric p_H	Whole Blood Carbon Dioxide p_H	Serum Carbon Dioxide p_H	Oxygen Capacity, per Cent by Volume	Oxygen Content, per Cent by Volume	Oxygen Saturation, per Cent	Blood Volume			Blood Volume per Kg.			Total Serum Protein, Gm.
									Blood, Ml.	Plasma, Ml.	Cells, Ml.	Blood, Ml.	Plasma, Ml.	Cells, Ml.	
1	2/14/27	40.5	7.49	7.39	7.37	19.4	18.5	95.0	1,466	1,000	466	97	65	32	73
1	2/19/27	37.5	7.41	7.43	7.41	19.8	17.3	87.0	1,375	922	454	98	67	31	74
2	2/21/27	40.5	7.49	7.37	7.35	15.0	8.2	54.6	2,125	1,607	522	91	69	22	105
2	2/25/27	37.5	7.50	7.47	7.45	20.7	19.1	92.0	1,869	1,320	548	84	59	25	104
3	2/21/27	40.5	7.41	7.34	7.34	16.8	12.2	72.6	1,188	880	308	92	68	24	65
3	3/1/27	38.0	7.47	7.44	7.44	20.8	12.8	61.5	985	685	299	80	56	24	52

recovery. Nevertheless, the divergence from neutrality is about the same as can be seen by the acidity ratio $\left(\frac{H^+}{H^+_n}\right)$. In other words, the hydrogen ion concentration increases during pneumonia, but due to the greater dissociation of water in to H^+ and OH^- at 41 C., the hydroxyl ion concentration increases in about the same proportion. This makes the acidity ratio remain essentially constant.

These values for the p_H of venous pneumonic blood in children are practically the same as has been found in adults. Thus, Hastings, Neill, Morgan and Binger [5] and Binger, Hastings and Sendroy [6] found the arterial p_H within the normal range but with a slight tendency to be on the alkaline side of the average normal value. Barach, Means and Bock [4] found low p_H values, but did not correct for the dissociation of water and thought that there was a tendency to acidosis in pneumonia. Buckman, Smith, Adams and Edwards [7] point out that there is a slight tendency for the $\left(\frac{H^+}{H^+_n}\right)$ ratio to be more alkaline during pneumonia, but since they did not correct the level of their curves for temperaure, the deviation is not so great as their values would seem to show. Appar-

ently, therefore, pneumonic blood in children and adults does not show significant disturbance in the neutrality regulation.

It should be noticed that the bicarbonate content of venous blood is lower than that reported in adults by Suderman, Austin and Camac. Although the present series of cases is too small for definite conclusions to be made, there seems to be a greater tendency to reduction of bicarbonate in children than in adults. This is in keeping with the fact that the blood reaction did not show the slight tendency to alkalosis seen in adults.

In table 2, volumes of blood are shown which were determined at the same time as the other studies reported in this article. These were reported in a previous study as cases 34, 33 and 32, respectively.[9] It should be noticed that the plasma volume decreases with the crisis in each instance, and that in cases 2 and 3 the diminution is considerable. In a previous study, it was shown that in pneumonia and probably fever in general, there is a moderate increase in the plasma volume and also in the storage of water throughout the body.

The increase in plasma volume during fever is indicated also by the lowering of the serum protein and hemoglobin concentration, as well as by actual determinations on the plasma volume. This increase in plasma volume, together with retention of fluid, is apparently the explanation of the chemical changes in pneumonia. Thus dilution of the plasma is sufficient to explain the low electrolyte concentration, and the general increase in body water is sufficient to explain in part the positive chloride balance. Hutchinson's [2] work would indicate that about one half of the chloride retained is to be accounted for by the pneumonic exudate. It would be desirable to have studies of the complete mineral balance in pneumonia together with such changes in weight as occur; however, it is not necessary to have a gain in weight during pneumonia to have an increase in body fluids. If the tissue cells lose volume and the water thus freed is not excreted, a true increase in body water without gain in weight may result. In such a case, the water freed from the cells would dilute the electrolyte of the lymph and tissue spaces and lead to retention of salt. This would be edema. Although a gain in weight during the course of pneumonia in children is not uncommon, the usual process is probably a dilution of body fluid by water freed but not excreted. If such were not the case, the relative starvation would lead to a considerable loss in weight in these patients.

Little can be said concerning the cause of the retention of water and the increase in plasma volume. In a prevoius paper,[14] a mechanism of water transport was described which involves the change in electrolyte

14. Darrow, D. C.; Soule, H. C., and Buckman, T. E.: Blood Volume in Normal Infants and Children, J. Clin. Investigation **5**:243, 1928.

concentration brought about by changing blood from an arterial to a venous environment. Thus the increase in the bicarbonate content of blood caused by increasing the carbon dioxide tension brings about a greater depression of the freezing point of about 0.001 C. for each volume per cent increase in carbon dioxide. Hence, if the arterial and venous bicarbonate contents are more widely separated than usual, one might expect an increase in the plasma volume. Buckman, Adams, Smith and Edwards [7] showed that the points for the arterial and venous blood tend to approach each other in adults with pneumonia. While points for arterial blood were not obtained in cases 1, 2 and 3, the character of the carbon dioxide absorption curves, together with the position of the points for the venous blood makes it probable that the points for the venous and arterial blood approach each other in children. Furthermore, the data of Suderman, Austin and Camac on adults point to dilution of blood. The mechanism which causes the change in plasma volume is not, therefore, likely to be the one mentioned.

Suderman, Austin and Camac [8] thought there might be an increase in the nonelectrolyte concentration after the crisis. They based this supposition on the increase in the ratio of the freezing point to the corrected conductivity. This ratio, however, does not take into account the change in water content of the serum. Thus a constant electrolyte concentration, as indicated by the corrected conductivity, would show a greater depression of the freezing point, the higher the protein content. This is due to the space occupied by the proteins. If the data of Suderman, Austin and Camac are recalculated in the manner used in this paper, a significant difference will not be found in the undetermined osmolar concentration before and after the crisis. For this reason, it does not seem likely that there is an increase in the nonelectrolyte after the crisis.

Palmer [15] and Clausen [16] showed that there is considerable increase in the urinary excretion of organic acids after the crisis. The data in this paper do not show any increased serum concentration of undetermined organic acid either before or after the crisis.

In a previous communication it was pointed out that a decrease in the electrolyte in the serum tended to be compensated for osmotically by retention of urea. It will be noticed that this does not occur in pneumonia, and that there is a considerable reduction in the osmotic pressure of the blood. It is not clear whether this is due to the short duration of the disease, or to some change in the chemical equilibria or renal activity brought about by high fever.

15. Palmer, W. W.: Acidosis and Acid Excretion in Pneumonia, J. Exper. Med. **26**:495, 1917.

16. Clausen, S. W.: The Excretion of Organic Acids after Pneumonia, Arch. Int. Med. **35**:571 (May) 1925.

SUMMARY

A study of the serum concentration of hydrogen ion, chloride, bicarbonate, protein, inorganic phosphate, lactate, total base, dextrose and nonprotein nitrogen, together with the freezing point was made in eight children before and after the crisis in primary pneumonia.

There is lowering of the concentration of chloride and bicarbonate, and since there is no compensatory increase in the nonelectrolyte, there is a decrease in the osmolar concentration indicated by the freezing point which is roughly parallel to the loss in osmolar concentraion of electrolyte. The total base concentration gives evidence that increased concentration of undetermined acids during the fever or after the crisis does not occur.

It is pointed out that the chief chemical changes in the blood during pneumonia may be explained by the increase in plasma volume and the tendency to retention of water throughout the body.

Three carbon dioxide absorption curves reveal that the level of the curves is low in pneumonia, and that the lower level is due to (1) the temperature effect and (2) lowered concentration of base.

The p_H is lower in pneumonia than normal, but the deviation from neutrality is about the same as normal, if the increased dissociation of water at higher temperatures is taken into account.

The serum during the fastigium and after the crisis does not show evidence of increase in the nonelectrolyte concentration.

HYPERTENSION IN THE YOUNG*

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Neither textbooks nor more comprehensive works on diseases of children have much to say about hypertension. Hecht,[1] in Pfaundler and Schlossman's Handbook on Diseases of Children, remarked: "Lasting increase of blood pressure is found particularly in cases of chronic nephritis, but also in scarlet fever nephritis after a few days. A further increase of blood pressure is often a precursor of uremia."

A number of children with increased blood pressure, ranging in age from 6 to 16 years, was examined and treated at the Mayo Clinic during a period of about eight years. The progress of the disease after dismissal could not always be ascertained, with the exception of a few recent reports, and necropsies were not obtained. Nevertheless, the twenty-five cases serving as a basis for this report offer features of significance.

According to Judson and Nicholson,[2] and Faber and James,[3] the systolic blood pressure does not exceed from 125 to 120 mm. of mercury in normal children under the age of 16 years. The figures of Alverez for the permissible systolic pressure at this age are 118 for girls and 127 for boys. The diastolic pressure in the tables of Judson and Nicholson does not exceed 64; in the tables of Faber and James it is higher and may reach 89 in girls 16 years of age. The elevations in blood pressure in my cases exceed the hitherto recognized permissible figures. The problem of the normal variations in blood pressure during childhood is not definitely solved and suffers from the lack of determinations on the same persons over a long period of time.

Renal involvement may exist without impairment of renal function, and renal insufficiency can be found without abnormal urinary constituents. Considering a phenol red return of 50 per cent or more, and blood urea of 30 mg. or less per hundred cubic centimeters, as indications of adequate renal function and more or less persistent albuminuria, presence of casts, erythrocytes and pus cells in degrees greater than 1, graded on the basis of from 1 to 4, as indications of renal involvement,

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* Submitted for publication, Aug. 8, 1928.

* Read before the American Pediatric Society, Washington, D. C., April 30 to May 2, 1928.

* From the Section on Pediatrics, the Mayo Clinic.

1. Hecht, A. F.: Erkrankungen des Herzens der Gefässe und Lymphknoten, Handbuch der Kinderheilkunde, ed. 3, Leipzig, F. C. W. Vogel, 1924, p. 661.

2. Judson, C. F., and Nicholson, Percival: Blood-Pressure in Normal Children, Am. J. Dis. Child. **8**:257 (Oct.) 1914.

3. Faber, H. K., and James, C. A.: The Range and Distribution of Blood Pressure in Normal Children, Am. J. Dis. Child. **22**:7 (July) 1921.

the cases, at the time of observation, may be classified as: (1) renal function adequate and urinary data negative, eight, and (2) renal involvement as indicated by the examination of urine or the determination of renal function, seventeen.

REPORT OF CASES

The first group is subdivided and includes cases from 1 to 8. The first three are cases of coarctation of the aorta, the more detailed description of which will be found in a publication by Blackford.[4] These were recognized by the discrepancies of pulse and blood pressure in the upper and lower extremities, and the relatively low diastolic pressure. There were pulsating superficial arteries on the thorax.

CASE 1.—Elevation in blood pressure had been noted when the boy was 12 years of age. A congenital lesion of the heart had been recognized much earlier. The chief complaint was ready exhaustion. The diagnosis of coarctation was not made until the boy was 15. At that time the pulse could not be felt in the abdominal aorta nor in the femoral arteries. The systolic pressure was 160 and the diastolic 70 in the right arm; in the left arm the systolic was 156 and the diastolic 82; in the right leg the systolic pressure was 108, and the diastolic 68. There was dilatation of the arteries in the interscapular space with a systolic thrill and dilated arteries above the costal margin. The heart was enlarged; the retinal arteries were contracted. Results of the examination of the urine were negative. On the administration of papaverine, the blood pressure dropped from 146 systolic and 70 diastolic to 118 systolic and 52 diastolic.

CASE 2.—A boy, aged 16 years, the previous year had been forbidden to play football by the school physician on account of enlargement and leakage of the heart. The boy had never had any subjective symptoms and seemed to be in good health. The pulsation of the abdominal aorta was weak. Superficial pulsating arteries were seen on the upper extremities and on the back. When the patient was reclining, the systolic pressure was 156 and the diastolic 60. The blood pressure was not obtainable on the leg; some oscillations of the manometer occurred between 60 and 88. The retinal arteries pulsated and were of small caliber. There was a congenital lesion of the heart. The urine was normal.

CASE 3.—A girl, aged 16 years, had had cardiac symptoms for three years. The systolic blood pressure was 160 and the diastolic 76, but she had an exophthalmic goiter, with a basal metabolic rate of + 62. This returned to normal after operation, but the systolic blood pressure was 176 and the diastolic 104. The blood pressure could not be determined on the leg. This and pulsating superficial arteries along the ribs and in the interscapular space led to the diagnosis of hypertension. The heart was enlarged; the retinal arteries were tortuous and relatively small in caliber. The urine was normal.

Case 4 illustrates a rise in blood pressure due to cerebral involvement.

CASE 4.—A boy, aged 7 years, had had an acute febrile disease diagnosed pneumonia about two months before admission. This was followed by restlessness

4. Blackford, L. M.: Coarctation of the Aorta, Arch. Int. Med. **41**:702 (May) 1928.

and insomnia, and later by convulsions. The systolic blood pressure was 170 and the diastolic 120. The stools contained blood for a few days. The rectal and vesical sphincter control was lost.

When the patient arrived at the clinic, he had convulsions on the right side, then paralysis of the right arm and progressing aphasia. Slight secondary anemia was present; the urine was normal; the blood urea was 20 mg. per hundred cubic centimeters. The retinal arteries were narrow, and the left optic disk was blurred, as if by receding edema. The highest systolic pressure was 175, the lowest 142; the highest diastolic pressure was 125, the lowest 113. An inflammatory lesion of the left temporal lobe producing softening of the brain was found at operation. Cloudy fluid, indicating ependymitis, was removed from the left lateral ventricle. The paralysis of the arm, the aphasia and the incontinence cleared up rapidly. Yet at the time of dismissal the systolic pressure was 166, the diastolic 116; the retinal arteries were narrow, and the disks had cleared.

On a return visit three months later, the systolic pressure was 100, the diastolic 60; the retinal arteries were still small. About eight months after operation, a physician reported the boy to be active and in good condition, with the systolic pressure 102, and the diastolic 68.

An increase in intracranial pressure can hardly be responsible for the elevation in blood pressure, because, in spite of the relatively short duration of the cranial involvement, the blood pressure did not return to normal immediately after operation, neither was the constriction of the retinal arteries relieved quickly.

Case 5 is one of questionable essential hypertension.

Case 5.—A girl, aged 10 years, had had mild sore throat about three months previous to admission to the hospital. The lower eyelids were puffy, and albuminuria had been found. Two weeks later albumin was not found in the urine, but a systolic blood pressure of 160, and a diastolic of 100 had persisted.

The hemoglobin was 80 per cent and the erythrocytes numbered almost 5,000,000. Examination of the urine gave negative results. The phenol red return was 80 per cent, the blood urea 24 mg., creatinine 1.6 mg. and uric acid 2.8 mg. per hundred cubic centimeters, respectively. The capillaries of the nailfold were narrow and the arterial limbs tortuous. The retinal arteries were somewhat tortuous and reduced in caliber. The highest systolic pressure while the patient was at the hospital was 166, the lowest 148; the highest diastolic pressure was 140, and the lowest 116. Hot baths did not have any effect on the blood pressure. The child was under a physician's care for a year, during which time her condition did not change. She did not have subjective complaints, and her general condition was good.

Cases 6, 7 and 8 probably are examples of the malignant hypertension syndrome of Keith, Wagener and Kernohan.[5]

Case 6.—A girl, aged 13 years, whose chief complaints were headache and vomiting, was admitted to the clinic. These attacks were of three years' duration, occurring at intervals of from three to four weeks, later at intervals of one week. She frequently had had epistaxis, lasting several hours; for a certain period it had

5. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

occurred two or three days every week. About four months before coming to the clinic, the patient began to have attacks of hematuria; these had occurred at intervals ever since and were sometimes profuse.

The patient was confined to bed for three months. The systolic blood pressure was 160. Facial weakness existed for six months, disappeared, and reappeared. The hemoglobin was 79 per cent, the erythrocytes numbered 5,000,000. The urine contained traces of albumin; a culture of the urine was negative. Further tests could not be made because the mother insisted that nothing more be done except a lumbar puncture, which had been advised elsewhere. The spinal fluid was under a pressure of 22.5 cm. of water, but was otherwise normal. The peripheral arteries were markedly sclerosed. Paresis of the left orbicular muscle and unilateral impairment of hearing made the neurologist suspect a lesion of a small cortical vessel in the pons. The retinal arteries were constricted; the optic disks were edematous; few cotton-wool exudates and hemorrhages were seen. The ophthalmologist characterized the lesion as graded 2, in the third stage of malignant hypertension. The systolic pressure varied from 218 to 186, the diastolic from 120 to 100.

Eight months later the patient was reported confined to bed without abatement of headache or vomiting.

Case 7.—This case was previously reported by Keith, Wagener and Kernohan. A girl, aged 15 years, had headaches that had begun four years previously; a year after their onset, they had become more frequent. She used glasses, but without relief. She had had influenza six months before coming to the clinic, and since that time had had attacks of nausea during the morning. She had fallen two months previously when running hurdles, which caused paralysis of the face, although she did not strike the ground with her head. She was nervous and troubled with enuresis.

When she arrived at the clinic, the facial paralysis had disappeared. The hemoglobin content on two occasions was 80 and 90 per cent, and the erythrocytes numbered 4,600,000 and 4,400,000. The peripheral arteries were definitely sclerotic. Sclerotic arteries in the edematous retina, edema of the disks and many cotton-wool exudates were visible. The urine contained albumin graded 2 and 4, but in the hospital it was never graded more than 1. A test for orthostatic albuminuria did not give a decisive result, because it could not be completed. Albuminuria, which was occasionally found on first examination and which disappeared later, was somewhat puzzling. The highest systolic pressure was 225, the lowest 188; the highest diastolic pressure was 145, the lowest 115. Baths, phenobarbital, nitrite, typhoid vaccine and a liver extract were administered; only the nitrite had any lowering effect on the systolic pressure.

The patient did not follow instructions about her care and after returning home she had severe nose bleeds, hematuria and tarry stools. She died a year later.

Case 8.—This case was also previously reported by Keith, Wagener and Kernohan. A boy, aged 9 years, began to vomit, sometimes forcefully, at intervals of from two to three weeks, five years before his visit to the clinic. One year later, headache accompanied these attacks, which gradually became more severe and more frequent. For five months he had had convulsions. The spinal fluid was reported at that time to be under increased pressure; the optic disks were choked, and the systolic pressure was 170.

The boy was apparently in good health. The hemoglobin content was 80 and 76 per cent; the erythrocytes numbered 4,700,000. Urinalysis and culture of the urine gave negative results. The phenol red return was 80 per cent on two occasions; the blood urea was 18 and 19 mg. and the creatinine was 1.7 mg. per hundred cubic

centimeters. The blood flow in the nailfold capillaries was rapid and the capillaries flickered. The retinal arteries were constricted, and there was chorioretinitis peripapillaris. The systolic pressure varied from 190 to 180, the diastolic from 130 to 114. The neurologist could not find evidence of a lesion of the central nervous system.

About nine months later it was reported that the headaches were more frequent and that decided peripheral sclerosis and enlargement of the heart were present. The optic disks were blurred, and extensive blotchy retinal changes were seen. The blood urea was 30 mg. and the creatinine was 1.5 mg. per hundred cubic centimeters. The phenol red return was 10 per cent. A single specimen of urine contained albumin. One month after examination the patient had a convulsive seizure at the breakfast table and died in stupor six hours later.

In cases 9, 10, 11, 12, 13 and 14, renal injury existed at the time of examination. In the first five cases, the renal lesion might readily have been secondary to a general vascular lesion, as in cases 6, 7 and 8. In case 14 such a possibility also existed, but the picture was rather complicated.

Case 9.—A girl, aged 8 years, complained chiefly of headache and vomiting, of two years' duration. The history was not reliable. For three years, she had been under a physician's care. The tonsils had been removed. The father said that the girl passed more urine than an adult, most of it at night, but did not drink an excessive amount of fluid. The urine was dark and sometimes contained much pus. Erythrocytes were not found until two weeks previous to examination, when the urine was bright red. Almost all food had been vomited during that time.

When the patient arrived at the clinic, palpable edema was not present, but the McClure-Aldrich test (the disappearing time of a bleb raised by the intracutaneous injection of 0.22 cc. of sodium chloride solution) was forty minutes. The hemoglobin on two occasions was 71 and 68 per cent, and the erythrocytes numbered 4,400,000 and 3,700,000. The odor of the urine was foul, and urine was voided at rare intervals in as large amounts as 750 cc. without residue. The condition was easily corrected with washings of an acriflavine dye. At first the urine contained albumin, graded 4, and was bloody; later the albumin and erythrocytes disappeared. Pus, graded 4, and innumerable colon bacilli were present. The phenol red return was 70 per cent; the blood urea was 36 mg., the creatinine 1.6 mg., and the uric acid 3.2 mg. per hundred cubic centimeters. The salivary urea index on two occasions was 32 and 45; later the blood urea was 19 mg. per hundred cubic centimeters. The blood cholesterol was 0.2 per cent. The child passed through an attack of jaundice. A direct van den Bergh test was made and the serum contained 7.4 mg. per hundred cubic centimeters. A roentgenogram of the kidneys, ureters and bladder showed small shadows in the region of the right kidney, although rather far out. The roentgenograms of the head showed digitation, but the spinal fluid pressure was not increased. The peripheral arteries were more tense than in most of the other cases. The capillaries of the nailfolds appeared normal on one side; it was difficult to see them on the other. The blood flow was rapid. Although the patient neither was cachectic nor had so-called red hypertension, the paradox reaction of Westphal[6] was not present. The retinal arteries were greatly constricted and sclerosed. There was resolving edema of the retina, but no hemorrhages. The systolic pressure varied

6. Westphal, Karl: Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes, Ztschr. f. klin. Med. **101**:545, 1924-1925.

between 202 and 164, the diastolic between 156 and 136; on talking or moving, both pressures rose readily from 20 to 30 mm. Chloral hydrate relieved the vomiting, and phenobarbital had a slight effect on the blood pressure. A piece of pectoral muscle was examined to determine the prognosis. The child died about four months after leaving the hospital.

CASE 10.—A girl, aged 12 years, had had a severe burn at the age of 2 years, followed by acute nephritis, with blood in the urine. She recovered and was in good health until she was 10 years of age, when she began to decline. She complained of headaches and enuresis.

The urine showed albumin, graded 2, but later the albumin was graded 1. The phenol red return was 60 per cent; the nonprotein nitrogen of the blood was 28 mg. per hundred cubic centimeters. There was an abnormality of the superficial veins in certain areas of the skin and of the capillaries in the nailfolds. The retinal arteries were reduced in caliber, and there was edema of the optic disks. The systolic pressure varied from 198 to 170, the diastolic from 155 to 120, read on the upper and lower extremities.

Two and a half years later, the hemoglobin was 70 per cent, the phenol red return was 40 per cent, the urine contained albumin, graded 2, and the blood pressure was unchanged. There was a gain in weight. A year later, the systolic blood pressure was reported 240 and 204, and the diastolic 140 and 120. The patient died five years after the first examination.

CASE 11.—A boy, aged 14 years, had attended school until one and a half years before coming to the clinic. He had been active, but often complained of headache. At that time, he became exhausted easily; the urine contained albumin; the systolic blood pressure was 220 and the diastolic 180. The diagnosis was acute endocarditis. The tonsils, adenoids and some teeth had been removed.

The hemoglobin content was 73 per cent; the urine contained albumin, graded 1. The concentration test was normal; the water test showed a lag, but the patient had been on a restricted fluid intake. The phenol red return was 40 per cent, the blood urea was 20 and 29 mg., the creatinine 1.6 mg. and the uric acid 2.3 mg. per hundred cubic centimeters, respectively. The nailfold capillaries were flickering and moderately constricted, with moderate disturbance of flow. The retinal arteries were constricted and tortuous. There were signs of hypertension with consequent arteriosclerosis. The basal metabolic rate was + 6. The systolic pressure varied from 204 to 164, and the diastolic from 158 to 108. Death occurred five years later.

CASE 12.—A girl, aged 10 years, had complained of headache and vomiting, which had begun one year previously and had become more frequent. A few days before her arrival, she had had severe cramps in the hands and feet, requiring morphine for relief.

The hemoglobin content was 56 and 66 per cent on two occasions; the erythrocytes numbered 3,400,000 and 3,900,000, and the leukocytes numbered 12,000 and 14,500. The urine contained albumin, graded 1, and pus, graded 2 and 3, with innumerable colon bacilli. The phenol red return was 50 per cent, the blood urea 30 mg., creatinine 1.2 mg. and uric acid 3.9 per hundred cubic centimeters, respectively. The retinal arteries were markedly constricted. The optic disks were edematous, and fatty macular stars were seen, but there were only a few hemorrhages. The blood serum was tested for pressure substances with rings of rabbit's intestine, with negative result. The systolic pressure varied from 170 to 124, and the diastolic from 180 to 130, on all extremities, and did not respond to any medication or baths. The child died two months after returning home.

CASE 13.—The chief complaint of a boy, aged 9 years, was convulsions. A year previous to his entrance to the hospital, headaches had begun to occur at night, about

twice a week; then they occurred more frequently. They were often associated with earache and fever. Six months later, vomiting, often projectile, had accompanied the severe headache. Then a right facial paralysis had occurred, followed by convulsions. Later the left eye had turned in, and for a few days vision in both eyes was affected. Two spinal punctures had been made, and the fluid was said to have been under increased pressure.

The liver and spleen were palpable. The urine contained albumin, graded 2. The phenol red return on two occasions was 15 and 10 per cent, the blood urea was 69 and 114 mg., the creatinine was 1.9 and 2.5 mg. and the uric acid was 4.2 and 10 mg. per hundred cubic centimeters, respectively. The nailfold capillaries flickered. The optic disks were choked with exudates and hemorrhages massing toward macula. The systolic pressure varied from 230 to 190 and the diastolic from 180 to 115. The patient died four months later.

Case 14.—A girl, aged 6 years, had been sick for eighteen months with attacks of vomiting, first at intervals of one week and then every second day. For five weeks she had had pains in the somewhat swollen joints of the extremities; later she had smothering spells, and for two weeks there was edema of the face and legs. The urine had contained some albumin and pus.

The patient was dyspneic and had considerable edema. The hemoglobin was 55 per cent, with from 3,700,000 to 4,000,000 erythrocytes. The urine contained albumin, graded 1, many pus cells and innumerable colon bacilli. The output was somewhat excessive for the child's age. The phenol red return varied; at one time it was 10 per cent, and on another occasion extremely slight. The urea was 39 and 29 mg. per hundred cubic centimeters. The left optic disk was slightly edematous on its lower border. There was a vitium cordis, the heart was large, and there was cardiac decompensation. The nailfold capillaries were normal. The peripheral arteries were sclerosed to a grade just exceeding 1. The systolic pressure varied between 190 and 150, the diastolic between 160 and 110.

After hospitalization, the edema disappeared and the cardiac decompensation, pyuria and bacteriuria improved, but the blood pressure was not affected. The child died about two months after leaving the hospital. The picture is complicated.

In cases 15 to 25, various renal disorders are associated with hypertension. In one of these, case 22, pyuria and the presence of colon bacilli were associated with unilateral headache. The whole group is not composed of homogeneous material, but a further subdivision is hardly possible.

Case 15.—A boy, aged 7 years, had had scarlet fever almost two months before he was admitted to the clinic. In due time, the hands and feet, and then the whole body, became edematous, and he became drowsy.

The hemoglobin was 67 per cent; it dropped to 38 per cent and rose again to 72 per cent. The erythrocytes numbered 3,300,000 and 4,400,000. The albumin and erythrocytes of the urine, at first graded 3 and 4, became a trace, and the casts, present at first, disappeared. The phenol red return was 50 and 40 per cent; the blood urea on the occasions was 117, 77 and 30 mg. per hundred cubic centimeters; the creatinine was 2, 2.4 and 1.4 mg. and the uric acid was 5.8 and 4.8 mg. per hundred cubic centimeters; later it was extremely low. The eyegrounds were normal. The systolic blood pressure had been 152 and the diastolic 104, but with general and urinary improvement the pressure gradually dropped to systolic 102 and diastolic 56 before the tonsils and adenoids were removed. At dismissal, the systolic pressure was 112 and the diastolic 64.

About three months later, the urine contained albumin, graded 1, and erythrocytes, graded 2, and the systolic pressure was 115 and the diastolic 70. Nearly two years later, a physician found albumin, graded 3; the phenol red return was 64 per cent and the nonprotein nitrogen of the blood was 51 mg. per hundred cubic centimeters. The urine had never been entirely free from albumin. The systolic pressure was 100 and the diastolic 80. A febrile attack with nasal symptoms prompted operation for ethmoiditis, which relieved the condition.

CASE 16.—A boy, aged 13 years, had been sick for one and a half years. After a febrile attack, swelling of the feet and legs set in, and the systolic pressure was 140 and the diastolic 96. Since then, he had suffered rather frequently from attacks of headache and vomiting.

On examination, there was a slight puffiness of the eyelids. The hemoglobin was 72 per cent; the erythrocytes numbered 4,100,000. The urine contained albumin, graded 2 and 3, and occasionally morphologic constituents. The phenol red return was 40 and 45 per cent; the blood urea was 52 and 58 mg., and the creatinine was 2.4 mg. per hundred cubic centimeters. The eyegrounds were normal. At first the systolic blood pressure was 190 and the diastolic 130; later the systolic pressure varied from 158 to 154, and the diastolic from 126 to 110.

It was reported that the blood pressure always remained high. The boy was treated for a time by physicians, who promised cures. He died about fifteen months after his dismissal from the clinic.

CASE 17.—A boy, aged 14 years, had had diphtheria at the age of 6. Since that time he had had pyuria, and, at intervals of months, attacks of nausea and vomiting, which recently had occurred more frequently.

There was edema of the scrotum and ankles. The hemoglobin was from 54 to 65 per cent; the erythrocytes numbered 3,300,000, and the leukocytes 11,600. The urine contained albumin, pus, erythrocytes, graded 2, and colon bacilli. Phenol red was not passed. The blood urea was 290 and 315 mg., the creatinine was 14.2 mg. and the uric acid was 7.6 and 8.3 mg. per hundred cubic centimeters, respectively. The optic disks were slightly edematous. The retinal arteries were constricted with some edema along their course. The systolic pressure varied from 154 to 174, the diastolic from 120 to 132. The patient left the clinic, and further reports could not be obtained.

CASE 18.—On a boy, aged 14 years, mastoidectomy had been performed two years before admission to the clinic. About seven months previously, he had had a cold followed by edema of the face and body. Pus and blood were found in the urine. The condition of the edema varied.

On the patient's arrival at the clinic, only slight puffiness of the eyelids existed, and the McClure-Aldrich test required one hour. The hemoglobin was 53 per cent, the erythrocytes numbered 3,500,000, and the leukocytes 11,300. At first the urine contained albumin, graded 3; later albumin was absent. The concentration test showed that the specific gravity varied between 1.014 and 1.019. The phenol red return was 35 and 60 per cent; the blood urea varied from 32 to 43 mg. per hundred cubic centimeters. The nailfold capillaries were constricted; the retinal arteries were mildly reduced in caliber. The blood pressure varied slightly: systolic, about 150; diastolic, from 95 to 100. The patient died about eight months later. A report stated that there was isosthenuria and gradual increase in blood urea to 58 mg. per hundred cubic centimeters.

CASE 19.—A boy, aged 15 years, had been sick for ten months. After a questionable case of scarlet fever, intense edema and severe albuminuria had developed. After rest in bed, the systolic pressure was 140. The tonsils had been removed.

Slight edema of the lower eyelids and ankles and some ascites were noted. The hemoglobin varied from 60 to 75 per cent; the erythrocytes increased from 3,300,000 to 5,000,000. At first the urine contained albumin, graded 3, and pus, graded 2, but they disappeared while the patient was in the hospital. The phenol red return was 40 per cent, the blood urea was between 40 and 62 mg., the creatinine 2.4 mg. and the uric acid was 4.1 mg. per hundred cubic centimeters, respectively. The optic disks were somewhat blurred; slight peripapillar edema was noted, and the retinal arteries were small in caliber. The systolic pressure varied from 184 to 130, and the diastolic from 130 to 70. The lower figures were obtained at the end of his stay in the hospital. The patient left the hospital, and further reports could not be obtained.

CASE 20.—A girl, aged 10 years, had destructive arthritis of the left hip and had acquired an abscess in the left groin. At this time, the retinal arteries were reduced, for her age.

About ten months later, the patient returned with draining sinuses in the hip and edema of the face and lower extremities. The hemoglobin rose from 60 to 78 per cent; the erythrocytes rose from 4,500,000 to 5,000,000; the urine contained albumin, graded 3; pus, graded 2, without growth of micro-organisms, and often erythrocytes, graded 2. The phenol red return was 65 per cent, the blood urea 19 mg., creatinine 1.5 mg. and uric acid 3 mg. per hundred cubic centimeters, respectively. The systolic pressure at first was 150 and the diastolic 95. With the disappearance of edema, the systolic pressure was 106 and the diastolic 54. When the patient was dismissed, the systolic pressure was 114, the diastolic 68 and the urine still contained erythrocytes.

CASE 21.—A boy, aged 6 years, had suffered from attacks of headache and vomiting for a year and a half, which gradually had become more severe.

Anemia was not present. The urine contained albumin, graded 2, with hyaline and granular casts, graded 2; these constituents disappeared. Culture of the urine showed 80 staphylococci for each 0.5 cc. The phenol red return was 65 per cent; the blood urea was 29 mg., and the uric acid was 3.3 mg. per hundred cubic centimeters. The eyegrounds were normal. The blood pressure gradually decreased from systolic 192 and diastolic 94 to systolic 92 and diastolic 52 at the time of dismissal. After the period of rest and the decrease in blood pressure, the headache disappeared, and the patient's condition improved.

CASE 22.—A girl, aged 10 years, had suffered from unilateral headache for one and a half years. Recently it had been continuous throughout the day.

The hemoglobin content was 64 per cent, and the erythrocytes numbered 4,500,000. The urine contained pus, innumerable colon bacilli and albumin, graded 1. The eyegrounds were normal. The systolic pressure varied from 136 to 130; the diastolic from 100 to 95. The patient was not hospitalized. Under treatment with sodium nitrite, the systolic blood pressure became 120, the diastolic 95, and the headache improved. The pyelitis also improved under treatment. The home physician gave endocrine treatment. The patient did not improve.

CASE 23.—A boy, aged 14 years, had complained of headache and edema of the face for a year. The urine had contained much albumin, which had persisted for a long time. There was congenital absence of the left eye.

The hemoglobin was 50 per cent, and the erythrocytes numbered about 2,400,000. At the first examination, the urine contained albumin, graded 3, but later it was graded only 1. The phenol red return was 5 per cent; the blood urea was 158 and 155 mg., creatinine 7.6 and 8.5 mg. and uric acid 3.8 mg. per hundred cubic centimeters, respectively. The peripheral vessels were sclerotic, graded 1 +. The

eyegrounds showed congenital abnormalities. The systolic pressure varied from 148 to 120; the diastolic from 80 to 60. The striking feature was the lack of subjective symptoms, in spite of the serious impairment of renal function. In view of the presence of other congenital abnormalities, the possibility of such an abnormality of the kidneys must be considered.

CASE 24.—A girl, aged 11 years, had had attacks of headache, sometimes associated with vomiting, for about two years, which had become more frequent and severe.

The patient was brought to the clinic for tonsillectomy only. The urine contained albumin and erythrocytes, graded 2. The phenol red return was 45 per cent; the blood urea was 36 mg. per hundred cubic centimeters. Chorioretinitis of the pigmented type and some vascular changes of hypertension were present. The basal metabolic rate was −7. The systolic pressure was 180, the diastolic 140. The patient left the clinic, and further reports were not obtained.

Severe vitium cordis with decompensation was the main clinical feature in case 25.

CASE 25.—A girl, aged 13 years, arrived at the clinic complaining of abdominal pain. The hemoglobin was 85 per cent; the erythrocytes numbered 4,500,000. The urine contained albumin, graded 2, hyaline and granular casts. The blood urea was 56 mg. and the creatinine was 1.5 mg. per hundred cubic centimeters. The heart and liver were enlarged, and dependent edema was present. The fundis of the eye presented moderately contracted arteries and venous compression. The systolic pressure varied between 160 and 140, and the diastolic between 115 and 110. The renal involvement was probably that of pronounced stasis. The administration of merbaphen promptly cleared up the edema. The blood pressure remained the same. This elevation in blood pressure in all probability is the type described in association with cardiac decompensation. The patient left the hospital against advice, and died shortly afterward.

COMMENT

Cases 6, 7 and 8 probably are of the type described by Volhard[7] "Das ischämische Endstadium des Nierensclerose" (the ischemic final stage of nephrosclerosis). Stress is laid on a renal lesion and its relation to the course of the disease, although its malignant character may be recognized at a time when impairment of renal function cannot be found. Objections have been raised against this intimate relation between the kidney and malignant hypertension.

The work of Wagener and Keith,[8] and Keith, Wagener and Kernohan,[5] led to the conclusion that a syndrome of malignant hypertension exists, characterized chiefly by persistent hypertension, absence of higher grades of anemia, adequate renal function at a time when striking lesions of the eyegrounds are visible and rapid fatal ending. The main histologic changes are situated in the small arteries and the arterioles,

7. Volhard, Franz: Die doppelseitigen hämatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1918, vol. 8, p. 576.

8. Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374 (Sept.) 1924.

while the larger arteries and the capillaries may be comparatively free from change. The most important and constant feature is the extreme diffuseness of the lesion; every organ, tissue and even the vessels of the gastro-intestinal tract and skeletal muscles are severely involved, sometimes the kidney, the heart, or the brain to a greater degree than the others. Such lesions were found in the pectoral muscle in case 9. The muscular coat was thickened; the lamina elastica was hypertrophied and split in places. In some arterioles, the intima is hyperplastic. These changes may be even more pronounced in other cases and in other organs. These changes can interfere with the blood supply to such an extent that they lead to secondary lesions in various organs. These injuries and their distribution explain clinical features.

The most striking illustrations of this syndrome of malignant hypertension is in case 8 in which, although the history dated back five years, signs of renal involvement had not occurred until a relatively short time before death, and then they were found only after careful search. In other cases, they made their appearance much earlier in the course of the disease. It must be regarded as well within the range of possibility that children can die of hypertension without any renal manifestations, if one judges by the experience of Keith, Wagener and Kernohan in cases of adults. The presence of renal involvement at a given time cannot be regarded as sufficient for a diagnosis of so-called nephritic hypertension. So far there are few cases belonging to this group, and the diagnosis is uncertain. Five other cases, 9, 10, 11, 12 and 13, probably should be included in this group. The mild changes in the eyegrounds about two months before death, the pronounced anemia, the low phenol red return, the preceding rheumatic infection, with a subsequent lesion of the heart and cardiac decompensation, make the picture of case 14 rather complicated, and hardly permit its inclusion in this group. Cases similar to the others have been described in the literature as hypertension of nephritis, for instance, one or two cases of Schwarz,[9] Berkley and Lee,[10] Beretervide and Pozzo,[11] Redwood [12] and Brill and Libman.[13]

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9. Schwarz, Herman: Kidney Diseases in Infants and Children: II. Malignant Hypertension Nephritis: Primary Sclerotic Kidney (Schrumpfniere), Am. J. Dis. Child. **27**:233 (March) 1924.

10. Berkley, H. K., and Lee, J. M.: Hypertension in Nephritis in Childhood, with a Study of Ninety-Three Cases, Am. J. Dis. Child. **13**:354 (April) 1917.

11. Beretervide, E. A., and Pozzo, F.: La nefritis hipertensina en la enfancia, Prensa méd. argent. **13**:453, 1926.

12. Redwood, F. H.: Chronic Hypertension Nephritis in a Child, Showing Unusual Neurological Symptoms, Virginia M. Monthly **53**:103, 1926.

13. Brill, N. E., and Libman, E.: A Contribution to the Subjects of Chronic Interstitial Nephritis and Arteritis in the Young and Family Nephritis; with a Note on Calcification in the Liver, J. Exper. Med. **4**:541, 1899.

The diagnosis in case 5 could not be other than essential hypertension. Examination of the urine gave negative results; the renal function was not impaired. Only slight changes in the nailfold capillaries and in the retinal vessels were noticeable, and subjective symptoms were absent. It is possible that this patient represents an early stage of malignant hypertension; at any rate, the hypertension was persistent, with relatively slight fluctuation.

This material contributes nothing toward the illumination of the old controversial problem of whether structural vascular changes are primary or secondary to a functional elevation in blood pressure.

The elevation in blood pressure in the presence of disease of the kidney has frequently been observed in children. It may be associated with diffuse types of glomerulonephritis following scarlet fever, as in case 15, or with other infections, as in cases 16, 17, 18 and 19, or with chronic interstitial nephritis, although in such cases high blood pressure is not a common occurrence, as stated by Greene.[14] The observations of Koch[15] are significant in regard to the connection of elevation in blood pressure and postscarlatinal nephritis. Albumin and other abnormal constituents of the urine never appeared without being preceded by elevation in blood pressure. A few similar observations had been reported by Kylin[16] in the course of tonsillitis.

In view of the frequent clinical associations of disease of the kidney, and increase in blood pressure, it is difficult to escape the assumption of a causal relationship, expressed by the term "hypertension of nephritis." In the classification of Kahler,[17] uncomplicated hypertension of nephritis is placed in the main group of functional hypertensions due to vascular contraction, and in the second subdivision with peripheral reflex hypertension. This reflex, rising from diffuse capillary injury, really represents an extrarenal factor. The classification of Kahler follows:

A. Functional hypertension
  I. Central
    (*a*) Primary
      (1) Psychic
      (2) Mechanical (increased intracranial pressure)
      (3) Lesional (organic lesions of the brain in the vicinity of vasomotor centers)
      (4) Toxic

14. Greene, C. H.: Chronic Diffuse Nephritis in Childhood, Am. J. Dis. Child. **23**:183 (March) 1922.

15. Koch, Fritz: Klinische Beobachtunger bei Scharlachnephritis, Ztschr. f. klin. Med. **102**:182, 1925-1926.

16. Kylin, Eskil: Sur quelques cas illustrant la pression artérielle dans l'état pré-néphritique, Acta med. Scandinav. **55**:525, 1921.

17. Kahler, H.: Die Blutdrucksteigerung, ihre Enstehung und ihr Mechanismus, Ergebn. d. inn. Med. u. Kinderh. **25**:265, 1924.

(*b*) Secondary
(1) Reflexly (from vessels or from organs)
II. Peripheral
(*a*) Primary
(1) Toxic
(*b*) Secondary
(1) Reflexly (peripheral reflexes arising from all vessels)
B. Anatomic hypertension
I. General or extensive organic constriction of the arterioles

The mechanism of this relationship remains obscure. The cases of malignant hypertension in this classification would come under the second main heading, that of anatomic hypertension, due to general or extensive organic constriction of the arterioles.

Case 4, in which the elevation in the blood pressure is referable to an organic lesion of the brain, could be accredited to the subdivision of central vasomotor stimulation. In this case, lesions possibly existed in the vicinity of vasomotor centers. The importance of such localization has been emphasized by Kahler, who acknowledged not only bulbar centers, but also centers in the region of the hypothalamus and a center near the motor region. Bordley and Baker [18] advanced the hypothesis that sclerosis of the arterioles supplying the brain stem, where the vasomotor centers are situated, can explain the hypertension which is necessary for an adequate supply of blood to the centers.

The group of interesting cases described by Blackfan and Hamilton,[19] in which the high blood pressure was associated with edema of the brain, would fit, according to the classification of Kahler, into the same main group and subdivision as in case 4, in which the high blood pressure was referable to an organic lesion of the brain. Instead of the lesional they would be of the mechanical type, in which the elevation in blood pressure is the result of increased intracranial pressure. Persistent cardiac decompensation seems to be the main cause of the high blood pressure in case 25. In case 14, cardiac decompensation was also present, but was not responsible for the hypertension. Although it improved decidedly, the blood pressure did not decrease, as will happen if its rise is due to cardiac decompensation.

So far as it was possible to ascertain, the blood pressure receded to normal in four cases (4, 15, 20 and 21). The first of these was an organic lesion of the brain cured by operation; the second was postscarlatinal nephritis; that of the third was associated with focal glom-

18. Bordley, James, and Baker, B. M.: A Consideration of Arteriosclerosis of the Cerebral Vessels and Pathogenesis of Hypertension, Bull. Johns Hopkins Hosp. **39**:229, 1926.

19. Blackfan, K. D., and Hamilton, Bengt: Uremia in Acute Glomerular Nephritis, Boston M. & S. J. **193**:617, 1925.

erulonephritis during the course of an infection; the elevation in blood pressure in the fourth was of rather obscure origin. The patients in cases 1, 2 and 3 are doing well; the patient in case 6 is extremely ill and confined to bed; the patients in eleven cases (7, 8, 9, 10, 11, 12, 13, 14, 16, 18 and 25) died within a period of from a few months to five years after leaving the clinic. Further information was not obtainable in cases 5, 17, 19, 22, 23 and 24.

Of the eight patients probably suffering from malignant hypertension, seven are dead and one is extremely ill. The history in this case (case 6) dated back three years, and the last report was obtained eight months after the patient left the clinic.

Counting from the time complaints were first noted, the duration of the disease in the fatal cases was, approximately, five years in case 7, six years in case 8, two and a half years in case 9, seven years in case 10, fourteen months in case 11, one and a half years in case 12 and sixteen months in case 13. In cases 10 and 11 the rise in blood pressure was noted early in the course of the disease. The duration of the disease in the case of cardiac decompensation (case 25) was three fourths of a year, in case 14 one and a half years; in the two cases of nephritic hypertension, it was two and three-fourths years in case 16, and sixteen months in case 18.

In these two cases, the eyegrounds were only slightly affected. In the other fatal cases, the retinal changes were more prominent. Of the remaining cases, in which the patients are believed to be living, lesions were not demonstrable in cases 15, 21, 22 and 23; vascular changes were found in cases 1, 2, 3 and 20; changes in the eyegrounds were moderate in cases 17, 19 and 24. Disturbances of vision were especially noted in cases 12 and 13. Headache was frequently complained of, alone in cases 6, 8, 9, 12, 13, 16, 21 and 24, and with vomiting in cases 7, 10, 11, 22 and 23; vomiting alone was recorded in cases 14 and 17. Headache and vomiting were the chief complaints in some cases. Symptoms emanating from the central nervous system were recorded in four cases. In case 6, there was impairment of hearing on the left and weakness of the left orbicularis muscle, a remnant of facial paralysis; and in case 7 also there was left facial paralysis. There was a history of convulsions in two cases (cases 8 and 13), and in case 13 there was left facial paralysis, and the left eye was rotated inward. This is the only patient of the series who was much undernourished. The symptoms suggested tumor of the brain, a suspicion strengthened by swelling of the optic disks of from 2 to 4 diopters. Increased blood pressure, however, does not occur often with tumor of the brain. In a series of forty-four patients in whom such tumors were verified, Hench found that this occurred only twice. In one of these cases, there was some evidence of arteriosclerosis, and the peripheral vessels of the retina were sclerotic. The rise in blood

pressure, cerebral symptoms and renal involvement in case 13 could be explained readily on the assumption of a generalized vascular lesion.

Tumor of the cerebrum was considered in some of the cases of Wagener and Keith, and decompression had been done elsewhere, without finding a tumor. A decompression was also done in the case reported by Redwood. In the cases of cardiac involvement, the heart was enlarged; in some of the others, the heart may have been slightly enlarged. Slight thickening of the peripheral arteries was noted in a number of cases, but this was graded more than 1 in only three cases (cases 9, 14 and 23), and was graded from 2 to 3 in cases 6 and 7. It is possible that cases with pronounced sclerosis of the larger arteries belong to a group by themselves.

The nailfold capillaries were not observed in all cases. Sometimes they were normal, sometimes the arterial limbs appeared somewhat constricted, and the loops tortuous, and the flow of blood was disturbed. But in only three cases (cases 8, 11 and 13) were the changes more pronounced, particularly in cases 8 and 13 in which the flow was rapid and the flickering striking, that is, capillary loops disappeared rapidly, as if they were jumping out of the field of vision.

Epistaxis during the course of the disease was noted in cases 6 and 7 and in both of these it was accompanied by hematuria. This occurred in case 9 also, but in this case other reasons enter into consideration. In case 7, tarry stools were reported before death. Passage of blood was noted also in two cases reported by Schwarz.

So far, treatment has been unsatisfactory. Hot baths, nitrates, phenobarbital, injections of foreign protein and liver extract have been employed. Occasionally, nitrite and phenobarbital effected an insignificant transitory fall in blood pressure. In one case, the nitrite test could not be finished because it aggravated the headache. Neither a strictly salt-free diet nor treatment with potassium has been employed in these cases. Blackfan and Hamilton obtained good results with intravenous injections of magnesium sulphate in cases of acute glomerular nephritis with high blood pressure and edema of the brain. Sometimes phlebotomy may be carried out. The general condition of some patients seemed to improve without any definite fluctuations of blood pressure, and at times the patients seemed to feel better with slight downward fluctuations of pressure. Lumbar puncture, performed in the clinic or elsewhere, did not have any striking effect. Most of the patients seemed to derive some benefit from the rest at the hospital, with its restriction of activity. Activity will aggravate headache, as is seen in the case of a girl (case 7) who was fond of exercise and indulged in swimming. The restriction of activity is also necessary in cases of coarctation of the aorta, even to the extent of complete rest in bed in some cases for short periods. The calorie-content of the diet given to the patients was

sufficient; the diet contained 1 Gm. of protein for each kilogram of body weight. Chloral hydrate seemed effective in cases of vomiting. Foci of infection and whatever complications exist should receive their proper treatment. The most important point in the treatment of patients with malignant hypertension is to restrict activity, with periods of complete rest. It is necessary to keep up the morale because the disease may last several years.

CONCLUSIONS

Different forms of hypertension, persisting for long periods, can occur in childhood. The cases reported here represent: (1) hypertension associated with coarctation of the aorta; in these cases the elevation in blood pressure is confined to the upper part of the body; (2) hypertension associated with cardiac decompensation; (3) hypertension intimately associated with disease of the kidney, in such cases it may be of shorter or longer duration, and at times be referable to increased intracranial pressure; (4) hypertension as the consequence of an organic cerebral lesion; (5) hypertension perhaps in the form of so-called essential hypertension, and (6) hypertension in the form of a syndrome of malignant hypertension as described by Keith, Wagener and Kernohan, with changes mainly in the small arteries and arterioles.

PULMONARY GANGRENE DUE TO SPIROCHETES AND FUSIFORM BACILLI *

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In 1905, Rona [1] discovered the presence of spirochetes and fusiform bacilli in smears taken at necropsy from the lungs of two patients with pulmonary gangrene. One year later, Castellani [2] reported two instances of hemorrhagic bronchitis, in which examinations of the sputum revealed large numbers of spirochetes. These authors were the first to recognize the importance of these organisms as causative agents of pathologic conditions of the respiratory tract. Since then, 150 cases of infection of the lower air passages by spirochetes, accompanied usually by fusiform bacilli, have been reported. The frequency with which these organisms appear as etiologic agents of pulmonary gangrene has been emphasized during recent years by Kline [3] and by Pilot and Davis.[4]

Infection of the respiratory tract by spirochetes and fusiform bacilli occurs much more often in adults than in children; it is said to appear nine times more frequently in the former. A survey of the literature reveals only six cases of pulmonary gangrene due to these organisms in children.

There has been much discussion concerning the origin of spirochetes capable of causing bronchial and pulmonary disease. Chalmers and O'Farrell,[5] Fantham,[6] Bloedorn and Houghton [7] and Levy [8] held that

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* From the Home for Hebrew Infants, Service of Dr. Alfred F. Hess.

1. Rona, S.: Zur Atiologie und Pathogenese der Plaut-Vincentschen Angina, Arch. f. Dermat. u. Syph. **74**:171, 1905.

2. Castellani, A.: Note on a Peculiar Form of Hemoptysis with Presence of Numerous Spirochaetae in the Expectoration, Lancet **1**:1384 (May 19) 1906.

3. Kline, B. S.: Spirochaetal Pulmonary Gangrene, J. A. M. A. **77**:1874 (Dec. 10) 1921; Fishberg, M., and Kline, B. S.: Spirochaetal Pulmonary Gangrene, Arch. Int. Med. **27**:61 (Jan.) 1921. Kline, B. S., and Blankenhorn, M. A.: Spirochaetal Pulmonary Gangrene, J. A. M. A. **81**:719 (Sept. 1) 1923.

4. Pilot, I., and Davis, D. J.: Studies in Fusiform Bacilli and Spirochaete: Their Rôle in Pulmonary Abscess, Gangrene and Bronchiectasis, Arch. Int. Med. **34**:313 (Sept.) 1924.

5. Chalmers, A. J., and O'Farrell, W. R.: Bronchial Spirochaetosis, J. Trop. Med. **16**:329 (Nov.) 1913.

6. Fantham, H. B.: Spirochaeta Bronchialis, Castellani, 1907, together with Remarks on the Spirochaetes of the Human Mouth, Ann. Trop. Med. **9**:391, 1915.

7. Bloedorn, W. A., and Houghton, J. E.: Bronchial Spirochetosis, J. A. M. A. **76**:1559 (June 4) 1921.

8. Levy, M. D.: Bronchopulmonary Spirochetosis (Castellani) New York M. J. **113**:186 (Jan. 29) 1921.

they are inhabitants of the bronchial tract and are not identical with the spirochete found so frequently in the oral cavity. Sufficient evidence has accumulated, however, to establish the fact that the spirochetes observed in pathologic conditions of the respiratory tract have originated from the buccal cavity. In most instances there are concomitant lesions in the mouth, such as carious teeth, ulceromembranous gingivitis, gangrenous stomatitis and Vincent's angina, smears from which reveal the presence of similar organisms. It has also been shown by Kline [9] that spirochetes and fusiform bacilli obtained from diseased conditions of the mouth when injected intrabronchially can produce gangrene of the lung in rabbits.

We have had the opportunity to observe a case of pulmonary gangrene caused by these organisms in a child, aged 3 years, which we considered worth recording on account of the paucity of reports of similar cases in the literature.

REPORT OF CASE

History.—A. S., a girl, aged 3 years, one of twins, who had weighed 3½ pounds (1.6 Kg.) at birth, was admitted to the institution at the age of 2 years; she weighed 18 pounds (8.2 Kg.) on admission, and her general condition was poor.

The father and mother were living and well. The twin sister had died of pneumonia at the age of 3 weeks. An older sister was an inmate of the institution and was considerably underweight. She had had two attacks of Vincent's angina during the previous winter, and had suffered from a chronic gingivitis.

The patient developed bilateral pneumonia a few days after admission. Three months before the present illness, the child had an attack of Vincent's angina which disappeared within a week following an intramuscular injection of 0.2 Gm. of sulpharsphenamine. She had had repeated attacks of pneumonia. The results of the Wassermann, Pirquet and Schick tests were negative.

Course.—On January 1, the child developed lobar pneumonia of the upper lobe of the right lung. The rise in temperature lasted only four days, returning to normal by crisis, but the physical signs of consolidation persisted. From January 16 to 30, the patient had a temperature ranging from 99 to 104 F.; physical examination at that time revealed a consolidation of the whole right lung. For the next six weeks the child did not have a rise in temperature, her appetite improved and she seemed to be enjoying fairly good health. The physical signs remained unchanged, however, and a diagnosis of unresolved pneumonia was made. During the next four weeks, that is, from March 13 to April 11, she was dyspneic and had a low grade fever. On April 1, examination of the chest showed that the physical signs had changed from dulness to flatness, and the breath sounds had become markedly diminished. A paracentesis of the right side of the chest yielded 50 cc. of serofibrinous fluid; four days later, 100 cc. was removed. Examinations of this fluid were negative for micro-organisms. Punctures of the chest during the following week failed to disclose the presence of fluid, although there was little change in the physical signs, and a diagnosis of thickened pleura was made. From April 11 to May 6, the patient again showed improvement, but soon after this period she declined rapidly; she was irritable, had a poor appetite and had a temperature

9. Kline, B. S.: Experimental Gangrene, J. Infect. Dis. **32**:481 (June) 1923.

ranging from 101 to 103 F. The cause of the fever was unknown, but naturally attention was focused on some process in the lung. Roentgenographic examination showed a diffuse shadow in the right half of the chest (fig. 1), and it was thought that the child had an encapsulated empyema. Repeated punctures, however, failed to obtain any pus, and it was then felt that the shadow on the roentgenogram was probably due to a thickened pleura and was masking some pathologic process in the lung. Tuberculosis was ruled out by the many negative Mantoux tests. Blood cultures and the Widal reaction were negative. A blood count showed: a leukocytosis of 30,000; polymorphonuclear leukocytes, 60 per cent; lymphocytes,

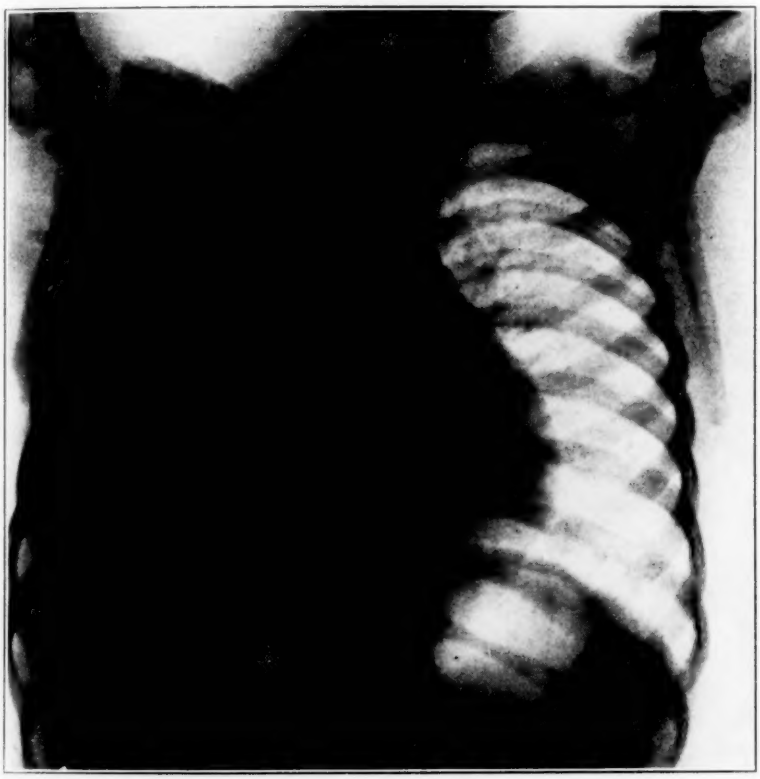

Fig. 1.—Dense shadow in the right half of the thorax with clear areas at the apex and at the periphery.

38 per cent; mononuclear leukocytes, 2 per cent; hemoglobin, 26 per cent, and erythrocytes, 2,250,000.

On June 14, that is, five and a half months after the onset of illness, a fetid odor to the breath was noted for the first time. A paracentesis of the chest was again performed, the needle being inserted deeply into the lung, and 2 cc. of a fetid, dark brownish fluid was obtained. A smear from this material revealed the presence of innumerable spirochetes and fusiform bacilli, and it then became obvious that the child was suffering from gangrene of the lung due to these organisms. Smears taken directly from the larynx also disclosed large numbers

of spirochetes and fusiform bacilli (fig. 2). Examination of smears from the tonsils and gums were negative for these organisms.

Sulpharsphenamine was given intramuscularly (0.2 Gm.), and was followed two days later by another injection. A transfusion of 300 cc. of blood was given by Dr. Lester Unger.

Two days after the aspiration of the fetid fluid from the lung, a cellulitis of the wall of the chest developed about the site of puncture. A large crucial incision exposed an extensive area of grayish black, fetid, gangrenous tissue, smears from which showed large numbers of spirochetes and fusiform bacilli. Local applica-

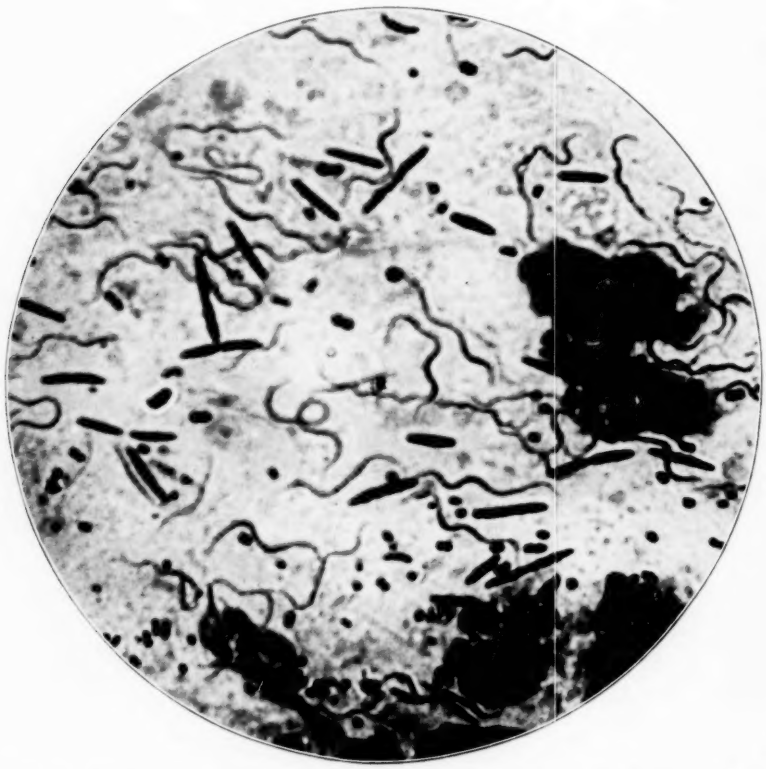

Fig. 2.—Microscopic appearance of sputum obtained from the larynx, showing numerous spirochetes and fusiform bacilli; × 1,200.

tions of a 10 per cent sulpharsphenamine solution were applied every four hours, and within forty-eight hours marked improvement was noted; the fetid odor disappeared and healthy granulation tissue appeared. At that time smears from the wound were negative for spirochetes and fusiform bacilli, which were apparently killed by the arsenical treatment. However, the general condition of the patient did not improve; the temperature remained septic, the loss in weight was marked and the child presented the picture of extreme cachexia. The use of arsenic was temporarily suspended because of the appearance of casts and albumin in the urine.

It was felt that the administration of sulpharsphenamine intramuscularly did not have any effect on the gangrenous process in the lung, because it did not reach

the affected portions in sufficient concentration. It was therefore decided to employ this form of therapy locally, and on June 31 an intercostal incision was made in the sixth interspace posteriorly. The pleural cavity was found to be obliterated, being replaced by dense fibrous tissue. After the latter had been broken through, gangrenous lung tissue was seen and could easily be shelled out by the hand of the operator. A tube was then inserted directly into the lung in order to make possible a direct flushing of the gangrenous tissue with an arsenical solution. Accordingly, 10 cc. of a 1 per cent sulpharsphenamine solution was injected daily. In spite of these measures, the child became rapidly worse and died on July 15.

Postmortem Examination.—Autopsy was performed eight hours after death. A postoperative wound was seen on the posterior aspect of the right side of the chest just below the scapular. The body was greatly emaciated. When an opening was made in the thorax, the left pleura was found to be slightly adherent at its base to the diaphragm. Free fluid was not seen in the pleural cavity. The lung was emphysematous, but was otherwise normal. On the right side, the pleural cavity was entirely obliterated by a densely thickened pleura. The medial portion of the lung was adherent to the pericardium. The whole right lung was replaced by necrotic tissue, which contained numerous small cavities. The cut surface of the lung presented a dark brownish appearance, and liquified necrotic tissue was seen oozing from its depth. The heart was normal, except for slight hypertrophy of the right ventricle. The liver was adherent to the diaphragm. It was enlarged and somewhat pale. The kidneys were normal in size, and a sharp demarcation could not be observed between the cortex and the medulla. The spleen was enlarged and congested. The rest of the abdominal organs did not show noteworthy changes.

Microscopic Examination.—The microscopic examination was made by Dr. W. C. Johnson. Sections were taken from various parts of the lung, including the necrotic regions, the walls of gangrenous cavities and also the parts less involved. In the most necrotic regions and in the lining of gangrenous cavities all trace of organized lung structure had disappeared, and only a pinkish staining granular and fibrillar material remained, in which occasional masses of brownish pigment and masses of bacteria could be seen. In the areas showing less complete disintegration the outlines of alveolar walls, bronchi and blood vessels could be faintly distinguished. Between the necrotic areas and the living tissue surrounding them, there was a rather narrow intermediate zone, in which the alveolar walls were in various stages of necrosis. In this zone, the cells lost their nuclear stain, and some were fragmented, but for the most part the outlines of the structures were preserved. In the living tissue surrounding the gangrenous areas, the alveoli were narrow and small, in many places almost atelectatic. The alveolar walls were thick, largely from the swelling of the alveolar epithelium, much of which had desquamated into the alveolar spaces. In some areas polymorphonuclear leukocytes were abundant, but most of the alveoli contained only desquamated epithelial cells, with occasional mononuclear cells and leukocytes. Little fibrin was present in any of the alveoli; it appeared mostly in the form of small, coarse masses. Some of the blood vessels in the walls of the necrotic areas contained thrombi. There was an extremely marked fibrous thickening of the interlobular septums, so that the lobules were distinctly demarcated and separated. Within the lobules, there was in places some fibrous thickening of the alveolar walls, but for the most part the fibrosis appeared to be interlobular. The pleura showed a moderate fibrous thickening.

The bronchial walls were infiltrated with lymphocytes, plasma cells, mononuclear cells and polymorphonuclear leukocytes. The epithelial lining had disappeared in those nearest the gangrenous cavities. In others, the bronchial epithelium was partly desquamated. The lumens contained granular débris and clumps of bacteria.

In one section from a portion of lung not necrotic, there was a patch of pneumonia, in which the alveoli were filled with mononuclear and polymorphonuclear leukocytes. Another section, in which there was no necrosis or pneumonia, showed thickening of the alveolar walls, apparently chiefly due to congestion and accumulation of mononuclear cells in the alveolar walls.

The epicardium contained a few polymorphonuclear leukocytes and mononuclear cells. At one point, a small mass of fibrin was adherent to the surface. The myocardium was practically normal. Between many of the fibers there were masses of bluish staining particles, apparently bacteria, but there was no reaction or necrosis around them.

Except for the cells at the periphery of the lobules, the hepatic cells contained numerous vascuoles, indicating fat. A few of the cells appeared coarsely granular —possibly necrotic. In many of the sinusoids there were considerable numbers of mononuclear cells, giving an appearance resembling leukemia.

The portal connective tissue was slightly infiltrated with lymphocytes. The cells lining the convoluted tubules of the kidney were pale, swollen and granular, suggesting cloudy swelling and possibly fatty metamorphosis. The pulp of the spleen was somewhat more cellular than normal. Small groups of cells with dark-staining cytoplasm suggested blood formation. The uterus, tube and ovaries were normal.

The diagnosis from microscopic examination was: (1) Gangrene of the lung, with interlobular fibrosis, partial atelectasis, and bronchopneumonia of the remaining portions; (2) slight acute pericarditis and (3) fatty metamorphosis of the liver.

COMMENT

Pulmonary gangrene never exists as a primary disease, but is seen especially in connection with pneumonia, aspiration of foreign bodies, general anesthesia, measles and scarlet fever. In our case, pulmonary gangrene appeared as a complication of pneumonia in a child who had had Vincent's angina three months previously, at which time presumably spirochetes and fusiform bacilli had been aspirated into the bronchial tract. These organisms probably existed in the lungs as saprophytes until the development of pneumonia, when, as a result of a lowering of local resistance, they acquired pathogenic activity. Spirochetes and fusiform bacilli have been aptly called "opportunists" by Pilot and Davis,[4] becoming pathogenic only when the integrity of the tissue with which they are in contact is altered. The importance of diminished local resistance in determining the pathogenic rôle of spirochetes and fusiform bacilli has been studied experimentally in animals. Kline [9] injected these organisms into the thigh of a guinea-pig without observing any unusual reaction; however, after traumatizing the thigh by means of a hemostat, a similar inoculation was followed by gangrene. It was neces-

sary for Vincent [10] and Pilot and Davis [4] to fortify these organisms with streptococci in order to cause gangrene of the pleura in a rabbit.

We have observed a number of children who have been suffering simultaneously from pneumonia and a spirillar infection of the mouth, and yet no complication occurred. However, the child who developed pulmonary gangrene was one of those in the poorest condition in the institution; she was markedly undernourished and the subject of repeated attacks of pneumonia. It would seem that in addition to spirochetes and fusiform bacilli in the lungs, a local predisposing cause, such as pneumonia, malnutrition and low vitality must be present for the development of pulmonary gangrene. An analogy in this respect may be drawn to noma, a disease due to these organisms, which occurs only in children in a state of poor nutrition and with feeble resistance.

In this connection, it is interesting to note the comparative frequency of noma and of pulmonary gangrene years ago. The former often occurred in institutions in epidemic form. In a monograph on pulmonary gangrene in children based on the study of sixty-five cases collected from the literature, Atkins [11] stated that pulmonary gangrene was seen in one of twenty-seven cases which came to necropsy; in about 30 per cent of these cases gangrene in other parts of the body, especially the mouth, was also observed. From the present knowledge one might deduce that spirochetes and fusiform bacilli were the causative organisms in cases of pulmonary gangrene associated with a similar process in the mouth. The high incidence of noma and pulmonary gangrene in children in former years may be attributed to the fact that the average institutional inmate was in poor physical condition, often marasmic and of low vitality. Today, on the other hand, the average child of an institution differs little physically from one brought up in the private home.

The characteristic symptoms of pulmonary gangrene—profuse, foul, brownish or greenish sputum and fetid odor to the breath—are most often missing in younger children. Consequently, the diagnosis of pulmonary gangrene in early childhood is extremely difficult, and, according to Holt,[12] is made generally only at autopsy. The knowledge, however, that spirochetes and fusiform bacilli are frequently the causative organisms may be of aid in the diagnosis of this condition even in the very young child. The presence or the previous history of an

10. Vincent, H.: Sur la fuso-spirochetose des voies respiratoires: Sa localization bronchique, Bull. Acad. de méd., Paris **96**:135, 1926.

11. Atkins, Louisa: Ueber Gangrena Pulmonum bei Kindern, Zurich, Orell, Fussli and Company, 1872, pp. 8 and 20.

12. Holt, L. E., and Howland, John: Diseases of Infancy and Childhood, New York, D. Appleton & Company, 1922, p. 553.

oral lesion due to these organisms in association with persistent elevation of temperature, cough, rapid loss in weight and physical signs indicating pulmonary involvement should make one suspect the existence of gangrene of the lung. A smear should be made directly from the larynx, and if these organisms are discovered in large numbers, a diagnosis of pulmonary gangrene is justifiable. If material cannot be obtained from the larynx for microscopic examination, we should advise a lung puncture, following Spano's [13] suggestion.

The presence of spirochetes and fusiform bacilli is of importance not only in establishing the diagnosis but also in the treatment of patients with pulmonary gangrene. These organisms yield rapidly to arsenic, and the most effective treatment is the intravenous or intramuscular administration of sulpharsphenamine, or similar preparations. Kline and Berger [14] have reported complete recoveries with this form of therapy, when it was begun during the early stages of the disease. In a late stage of the disease, however, treatment is of little if any avail.

As a prophylactic measure against pulmonary gangrene, the value of oral hygiene should be emphasized, since spirochetes and fusiform bacilli are more abundant in the mouth when it is unclean. Vincent's angina and ulceromembranous gingivitis are common conditions in institutional children and should receive prompt treatment. The local application of a 10 per cent sulpharsphenamine solution in conjunction with 0.2 Gm. administered intramuscularly is a satisfactory form of treatment. The importance of good nutrition in the prevention of pulmonary gangrene cannot be stressed too strongly.

SUMMARY

A case of pulmonary gangrene due to spirochetes and fusiform bacilli is reported in a child, aged 3 years.

The presence of spirochetes and fusiform bacilli in smears taken directly from the larynx and from the fetid material obtained by lung puncture was instrumental in making the diagnosis.

The importance of oral hygiene, prompt treatment of spirillar infections of the mouth and good nutrition in the prevention of fusospirochetal pulmonary gangrene is emphasized.

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14. Kline, B. S., and Berger, S. S.: Spirochaetal Pulmonary Gangrene Treated with Arsphenamines, J. A. M. A. **85**:1452 (Nov. 7) 1925.

Case Reports

MUSCULAR HYPOTONIA ASSOCIATED WITH CONGENITAL HEART DISEASE*

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Numerous anomalies of the nervous system other than mental deficiencies or derangement of the central nervous system associated with congenital heart disease have been described,[1] such as: abnormal conformations of the skull, spina bifida, hydrocephalus, anencephaly, facial paralysis, ptosis and bilateral micro-ophthalmus. Muscular hypotonia associated with congenital heart disease has heretofore not been reported.

Normally, hypotonia is frequently found persisting in infants up to the age of 9 or 10 months. If it continues after this age and the child is unable to hold its head erect or later is unable to walk, a pathologic condition should be suspected. A frequent and well defined pathologic state of hypotonia is found in amyotonia congenita, or Oppenheim's disease.[2] This condition, which occurs in children in the first year of life, manifests itself by a marked hypotonia of the muscles. They are in an extreme state of flaccidity, feel weak and soft and are thinner and smaller than normal, although they are not atrophic in appearance. These muscles are not totally paralyzed; they always show some voluntary contractions. The extremities are most frequently involved, those of the lower more marked than the upper. The knee reflexes are absent. The electrical reactions show qualitative changes; there is a diminution in the faradic stimulus with the ability to bear strong faradic currents and a normal galvanic response. An important characteristic of this disease is a tendency toward a progressive amelioration.

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2. Oppenheim, H.: Ueber allgemeine und localisierte Atonie der Muskulatur (Myatonia) im fruhere Kindesalter, Monatschr. f. Psychiat. u. Neurol. **8**:232, 1900; Ueber einen Fall von Myatonia Congenita, Berl. Klin. Wchnschr. **10**:255, 1904.

Fig. 1.—Marked hyperextension of the extremities.

Fig. 2.—Marked abduction of the hips; the dorsum of the foot is in contact with the tibia.

Fig. 3.—Dorsiflexion of the knees and ankles.

In certain cases of bilateral infantile cerebral hemiplegia with or without athetosis, there may be an excessive muscular hypotonia as intense as in amyotonia congenita, but disturbances are not present in the electrical reactions. The tendon reflexes are exaggerated, and there is a positive Babinski reaction.

Other conditions associated with hypotonia are Friedreich's ataxia, cerebellar diseases, chorea, infantile paralysis, occasionally Pott's disease, syringobulbia, labyrinthine vertigo and tabes dorsalis.

The following case of hypotonia apparently is not associated with any of the pathologic entities mentioned. It is, however, associated with congenital heart disease. Since this association has never been described, this case is reported.

Fig. 4.—Hyperextension of the hips with the feet brought in back of the neck.

REPORT OF CASE

History.—G. S., a Jewess, aged 4½ years, was admitted to Montefiore Hospital on Jan. 30, 1928, complaining of inability to walk and of shortness of breath. The family history was essentially negative. The child was a full term infant; the labor lasted from five to six hours and ended in a normal delivery. At the age of 3½ years, she had scarlet fever and chicken-pox. Four days after birth, because of intense cyanosis, a diagnosis of congenital heart disease had been made. Subsequently, she had become extremely dyspneic and cyanotic on the slightest exertion. She had never walked nor stood unsupported, because any such attempts caused extreme dyspnea and cyanosis. Four months before the patient's admission, the parents had become concerned over her inability to walk, which resulted in her admission to Mount Sinai Hospital, from which place she was discharged without improvement.

Fig. 5.—Eversion of the feet and legs.

Fig. 6.—Abduction of the thighs, flexion of the calves, with eversion of the plantar surface of the foot.

Examination.—The patient was a fairly well nourished, but slightly underdeveloped, child. There was extreme cyanosis of the entire body, especially of the face and extremities. She was able to sit up in bed, hold her head erect and stand when supported, but was unable to walk. The anterior fontanel was open but did not pulsate. The circumference of the head was 50 cm. There was a slight occipital flattening. There was moderate bilateral exophthalmus, especially of the right eye with ptosis of the left upper lid (fig. 4). The palpebral veins were prominent. There was some weakness of the left external rectus muscle. The pupils were regular and equal and reacted to all stimuli. The fundi showed engorgement of the retinal vessels with a depression of the optic disks. There was a slight weakness of the left side of the face. The teeth were in poor condition. The lips and tongue were extremely cyanotic, and the pharynx was markedly congested. On the right side, the vessels of the neck, especially just

Fig. 7.—Overextension of the wrists; exophthalmus of right eye; ptosis of the left upper lid.

above the suprasternal notch, showed marked pulsations. The sternum was prominent, and there was a definite bulge of the right half of the thorax. The lungs were clear. The apex of the heart was visible and palpable in the fifth left intercostal space at the midclavicular line. A diastolic shock was felt over the precordium. Thrills were not palpable. On percussion, there was enlargement to the left and at the base. A harsh systolic murmur was audible at the second and third left interspace and transmitted over the precordium. The second sound was markedly accentuated, especially at the pulmonic area. The rate was 110 per minute, and the rhythm was regular. The abdomen was normal. There was a marked clubbing of the fingers and toes.

There was a marked flaccidity of the muscles, especially in the upper and lower extremities. These muscles felt normal but were atonic. On palpation, the skin, subcutaneous tissue and underlying muscles could be separated and did

not have a velvety-like sensation. There was not any wasting, apparently, in any group of muscles or individual muscle. The contour of the limbs was not altered. The muscles of the face and neck seemed to be of fairly good tonus. The head was maintained in the erect position. The child was able to sit up and assume any position commanded, but was unable to walk, although the voluntary power of the muscles was retained. The ligaments seemed to be completely

Fig. 8.—Extreme flexion at the wrists.

Fig. 9.—Marked dorsiflexion; the dorsum of the hand is touching the forearm.

relaxed, and the limbs could be placed in any position without eliciting pain or causing any discomfort. The lower extremities were in a condition of extreme flaccidity and hyperflexibility (figs. 1, 2 and 3). They could be brought with ease to the back of the neck (fig. 4). The feet and calves could be completely everted (figs. 5 and 6). The feet could be placed in a position in which the dorsum touched the front of the tibia (fig. 2). The hands were also in an

extreme state of flaccidity and could perform loose movements (fig. 7). The wrists could be flexed (fig. 8) and extended to the utmost degree. The hyperextension of the wrist was such that the fingers and the dorsum of the hand could be placed in contact with the back of the forearm (fig. 9). Fibrillary contractions were not present. All the deep reflexes were moderately increased but equal, the abdominal reflexes were present and there was neither a Babinski nor an allied reflex. The sensation was not impaired. The sense of position as well as the bone and joint sensibility were intact. The electrical reactions were normal. The muscles responded to both faradic and galvanic currents. It was not necessary to use a strong faradic current to produce a strong contraction. The mentality of the child was fairly normal.

X-ray examination of the chest showed an increase in the lung markings due to pulmonary congestion, especially on the right side. The heart was horizontal in position, enlarged to the right and left, especially in the region of the left ventricle. There was a slight widening of the superior mediastinum, probably the result of the widening of the vascular trunk on the right side, including the superior vena cava. A thymic shadow was not present. The bones of the hands and feet did not show any abnormalities. There was a marked clubbing of the fingers and toes.

The electrocardiogram showed a right ventricular preponderance. The P and QRS waves in leads 1 and 2 were unusually high.

Examination of the blood revealed: red blood cells, 6,184,000; hemoglobin, 164 per cent; white blood cells, 8,400; polymorphonuclears, 44 per cent; lymphocytes, 42 per cent; large mononuclears, 3 per cent, and transitionals, 1 per cent. The results of a urinalysis were negative. The Wassermann reaction and the results of an examination of the spinal fluid were negative.

COMMENT

As is readily seen, this case presents diagnostic difficulties. The cardiac condition does not admit of difficulties. The intense cyanosis present since birth, the clubbed fingers, the cardiac enlargement with a systolic blow at the base and the characteristic electrocardiogram, all point to congenital heart disease. The important picture is the extreme state of hypotonia of the muscles of the extremities. Is this an anomaly associated with a congenital cardiac condition, as other anomalies found, or is it totally independent of the heart disease?

The only disease that this case of hypotonia simulates is amyotonia congenita. Against the diagnosis of amyotonia is the ability to palpate separately the skin, subcutaneous tissue and the muscle, the lack of velvety feeling of these structures, the absence of a padlike foot, the ability to hold the head erect, the greater preservation of the voluntary power of the muscles, the presence of all the deep reflexes, the absence of a thymic shadow and the normal responses to electrical stimulation. On the other hand, late and improved cases of amyotonia congenita begin to show a return of the deep reflexes and an improvement in the power of the muscles. From this it could be concluded that the condition may be an atypical form of amyotonia congenita.

The hypotonia in this case cannot be explained on the basis of posterior column disease, as there were no disturbances in the position or the bone and joint sensibility. The flaccidity cannot be explained on the basis of diseases of the anterior horn, as the reflexes are normal and atrophy of the muscles is not present. The other neurologic disturbances, the bilateral exophthalmus and the ptosis of the left upper lid, suggest that the hypotonia is an associated anomaly.

CONCLUSION

A case of congenital heart disease associated with a marked hypotonia is reported.

If the hypotonia is an anomaly, as others occurring in a congenital cardiac condition, then this is the first case of its kind reported. If the hypotonia does not have a relationship to the cardiac condition, the only disease that it simulates is amyotonia congenita, in which case it would be an atypical form of this entity.

PRELIMINARY EXPERIMENTAL STUDY ON THE CAUSE AND THE CURE OF ORTHOSTATIC ALBUMINURIA *

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One of the intermittent albuminurias, generally known as orthostatic albuminuria or orthose, has in the past been the subject of intensive study by a great many investigators whose theoretical conceptions have often been the subject of discussions among medical, as well as among biologic, authors.

Among the many hypotheses are those indicating a mechanical circulatory disturbance, a vasomotor disturbance, asthenia, an internal secretory anomaly or several combining disturbances as the causes of the phenomena mentioned.

Without going into a discussion of those various hypotheses and theories for the time being, the outcome of some clinical experiments will be explained here.

REPORT OF CASES

CASE 1.—S. Z., a school boy, aged 12 years, was seen on July 10, when he had symptoms of scarlet fever, i. e., he vomited and had sore throat and fever. On July 11, he had rash and fever. He was admitted to the hospital on July 12 with an eruption of the skin that extended over the body and extremities.

After the patient had been under treatment from July 12 until July 30, and had entered the convalescent period, I took him under observation and ordered a specimen of urine taken at 7 p. m. on the 30th for examination. The child also was ordered not to take any milk from 2 to 7 o'clock of that day. It was found that the specimen was free from albumin and had a specific gravity of 1, was colorless and had epithelial cells and leukocytes. The specimen taken at 5 a. m. of the next day did not show any albumin. The specimen taken the night of the same day and that taken at 5 a. m. of the next day had an albumin content of 3 plus. The patient was ordered not to receive any milk from 2 p. m. on August 1 until lunch time on August 2. This experiment resulted in the absence of albumin in the specimen taken at 7 p. m. on August 1 and in that taken at 5 a. m. on August 2, but calcium oxalate crystals were present in both specimens. However, although he had not taken any milk until noon on August 2, the specimen had at that time an albumin content of 3 plus, but no calcium oxalate crystals. This was a case of excretion of calcium oxalate without albumin, followed by another case of excretion of protein without calcium oxalate and vice versa. The excretion of these substances, however, makes plausible the possibility of a nonequilibrium between phosphorus, calcium, magnesium and hydrogen ion concentrations and albumin or protein in such cases.

The specimen taken at 7 p. m. gave an albumin content of 1 plus, while that taken at 5 a. m. on August 3 was negative. In the specimen taken at 7 p. m., however, an albumin content of 3 plus was found, and the specific gravity was

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1.25, while the specimen taken at 5 a. m. on August 4 was negative and had a specific gravity of 1.12, giving, thereby, the evidence that the normal function of the kidney was established at that date. While the specimen taken in the morning of August 5 gave a negative reaction, the specimens taken at noon, August 4 and 5, had an albumin content of 3 plus and the specimens taken at 7 p. m. on both days had an albumin content of only 1 plus.

The specimens taken at noon showed more albumin, because of the fact that the child was more active in the morning than in the evening. Furthermore, rest in the afternoon and the difference between the morning, noon and evening diets may have had some effect.

The fact that the picture of the health situation of the child had changed entirely, as far as the microscopic analysis was concerned, is interesting. Although I could not find casts in the specimens examined from July 30 to August 3, the specimen taken at noon on August 4 showed a content of 2 plus for casts and cylindroids, until August 10, when neither casts nor cylindroids were found. This nephritic disturbance, however, did not interfere with the orthostatic phenomena of albuminuria.

The child was given four cups of milk during the nights of August 3 and 4. Not a trace of albumin could be found in the specimen taken at 5 a. m. on August 4. The specimens taken at noon on August 4 and 5 gave an albumin content of 3 plus and those taken in the evenings of both days gave an albumin content of 1 plus. The outcome of the chemical analysis of the specimens taken in the mornings and evenings of August 6 and 7 were the same as the preceding day, with no albumin in the early part of the morning before breakfast and a content of 2 plus at 7 p. m. On August 8, three specimens, taken at 5 a. m., 4 p. m. and 7 p. m., were examined. It was found that the specimen taken at 5 a. m. was negative as on the preceding days and the other two showed an albumin content of 2 plus.

Blood was taken from the patient on the afternoon of August 8 and was analyzed for its content of calcium and phosphorus. It was found to contain 9.2 mg. of calcium and 7.8 mg. of phosphorus. Thus, there was an excess of phosphorus.

The specimen of urine taken at 5 a. m. was negative, while that taken at 7 p. m. had an albumin content of 2 plus.

The child was given a few glasses of diluted calcium hydroxide during the day of August 14. The result was that the specimen taken at 7 p. m. gave a negative reaction, while that taken at 5 a. m. of the next day was negative like those of the preceding days. The albuminuria was suppressed at least for that particular day. As the child was not ordered to continue the treatment with calcium hydroxide, the albuminuria started again. On August 17 I found 2 plus of albumin in the specimens taken at noon and in the evening. From August 18 until August 22, however, the child continued the intake of diluted lime water, and the specimen of urine was tested three times a day, with a negative result. After that date, treatment with lime water was discontinued, but the finding of protein in the specimen remained negative.

Case 2.—V. C., a man, aged 22, a fur dyer, was brought to the hospital on Aug. 19, 1927, suffering from varicella. The general condition was good. The patient was placed on a soft diet; he slept well during the time of illness, and did not have any complaint during his treatment in the hospital. While convalescencing in the ward, the patient always sat up during the day. Specimens of urine were taken for examination on the days and hours as stipulated in table 2.

TABLE 1.—*Results of Examination of Specimens from July 30 to August 22*

Date	Time	Reaction	Specific Gravity	Albumin	Oxalates	Casts, Cylindroids	Leukocytes	Epithelial Cells
			Case 1, S. Z.					
July	30, 7 p.m.	Neutral	1.00	None	None	None	None	None
	31, 5 a.m.	Acid	0.05	None	None	None	None	None
	31, 7 p.m.	Acid	0.18	++	None	None	None	None
August	1, 5 a.m.	Acid	0.08	++	None	None	None	None
	7 p.m.	Acid	0.10	None	++	None	None	None
	2, 5 a.m.	Acid	0.12	None	++	None	None	None
	noon	Acid	0.15	+++	None	None	None	
	7 p.m.	Alkaline	0.10	+	+	.....	.....	None
	3, 5 a.m.	Slight acid	0.10	None	.....	.....	.....	+
	7 a.m.	Acid	0.25	+++				
	4, 5 a.m.	Acid	0.12	None				
	noon	Acid	0.22	+++	None	++	++	+
	7 p.m.	Acid	0.18	+	None	+	+	+
	5, 5 a.m.	Alkaline	0.04	None	None	+	+	+
	7 p.m.	Alkaline	0.12	+	None	+	+	+
	6, 5 a.m.	Alkaline	0.10	None	None	+	+	+
	7 p.m.	Acid	0.16	+	None	+	+	+
	7, 5 a.m.	Acid	0.10	None	None	None	+	+
	7 p.m.	Acid	0.22	++	None	+	+	+
	8, 5 a.m.	Acid	0.08	None	None	None	None	+
	4 p.m.	Acid	0.23	++	+	Cylindroid +	+	+
	7 p.m.	Acid	0.28	++	+	Casts ++	+	+
	9, 5 a.m.	Acid	0.10	None	None	+	+	+
	noon	Acid	0.15	+	None			
	14, 7 p.m.	Alkaline	0.32	None	None			
	15, 5 a.m.	Slight acid	0.08	None	None			
	17, noon	Acid	0.05	++	None	None	None	None
	7 p.m.	Acid	0.16	++	None	None	None	None
	18,5 a.m.	Acid	0.12	None	None	None	None	+
	noon	Acid	0.10	None				
	7 p.m.	Acid	0.10	None				
	19, 5 a.m.	Acid	0.16	None				
	21, 7 p.m.	Acid	0.25	None	None	+	+	++
	22, 5 a.m.	.....	0.10	None	None	+	+	+++

TABLE 2

Date	Time	Reaction	Specific Gravity	Albumin	Oxalates	Casts, Cylindroids	Leukocytes	Epithelial Cells
			Case 2, V. C.					
August	14, 7 p.m.	Acid	....	+				
	15, 5 a.m.	Acid	1.08	None				
	15, 1 p.m.	Slight acid	0.09	++	None	None	None	+
	15, 7 p.m.	Neutral	0.10	+	None	None	None	+
	16, 5 a.m.	Slight acid	0.06	None	None	None	+	+
	16, 7 p.m.	Slight alkaline	0.10	++	None	None	+	+
	17, 5 a.m.	Acid	0.11	None	None	None	None	+
	17, noon	Slight acid	....	None	None	None	None	+
	17, 7 p.m.	Acid	0.16	++	None	None	None	+
	18, 5 a.m.	Acid	0.10	None	None	None	None	+
	18, 7 p.m.	Acid	0.20	+	None	None	None	+
	19, 5 a.m.	Acid	0.15	None				
	19, noon	Acid	0.07	++				
	19, 7 p.m.	Acid	0.16	+				
	20. 5 a.m.	Acid	0.15	None	None	None	+	+
	20, noon	Acid	0.04	+	None	None	+	+
	20, 7 p.m.	Slight alkaline	0.07	++	None	None	+	+
	21, 5 a.m.	Acid	0.10	None	None	None	+	+
	21, 7 p.m.	Acid	0.15	++	None	+	+	+
	22, 5 a.m.	Acid	0.09	None	None	+	+	+
	22, 1 p.m.	Acid	....	None	None	+	+	+

It was found that the specimens taken in the evening, at 7 p. m., had a 2 plus content of albumin, while those taken in the early morning gave a negative reaction.

On August 17, the patient fasted during the morning, from 5 a. m. until noon, taking only water. The specimen of urine taken at noon gave a negative reaction for albumin. The specimen taken in the evening, at 7 p. m., however, gave a positive reaction, showing an albumin content of 2 plus.

This experiment suggests that the posture of the patient cannot be the direct cause of the disorder, but acts only mechanically, and that the real cause may be in connection with the metabolic processes, stimulated probably by the nervous system.

Another experiment was made on August 19. The patient was ordered not to eat anything, but to drink as much milk as possible from 5 a. m. until noon. The chemical examination of the specimen of urine taken at noon, before lunch, showed an albumin content of 2 plus. The striking evidence between the intake of only milk and the intake of only water, in regard to the symptom of orthostatic albuminuria, compelled me to believe that the excretion of albumin may be due to the absence of a sufficient amount of a certain chemical element in the blood stream or in some other organ which would keep its equilibrium with the amount of excreted or secreted protein colloidal substances of the milk.

In order to check my results obtained thus far, a specimen of blood was taken from the patient, in the afternoon of August 18, and was analyzed for calcium and phosphorus. It was found that the blood contained 11.2 mg. of calcium and 3.9 mg. of phosphorus. Those are, of course, normal figures, but even in cases in which an equilibrium of calcium-protein may not be present—as will be seen—there was apparently not enough calcium to maintain, physicochemically speaking, an equilibrium of calcium and protein.

In order to find out whether or not there might be such an equilibrium, an experiment was undertaken with the intake of diluted calcium hydroxide. The patient was given ordinary diluted lime water at 10 a. m. and at noon on August 22. Not a trace of albumin was found in the specimen taken at 10 o'clock. Although the patient was discharged at 1 p. m. of that day, after the specimen had been taken, the evidence demonstrated that there was need of calcium, and that the original cause was the unbalanced state of calcium-protein substances, as in case 1. The evidence also suggested that an equilibrium between calcium and protein, calcium and phosphorus, calcium and magnesium and phosphorus and protein, is of great importance and necessary for the existence of a proper balance between organic and inorganic substances in the blood stream or in the fluid of some other organ of a person, especially a person of the physical condition and age of the patient.

The fact is interesting that although albuminuria or excretion of protein substance took place during the day, from August 14 until August 22, the test for calcium oxalate was always negative, which gives the evidence that oxaluria does not necessarily accompany albuminuria.

COMMENT

The intake of soluble calcium, as for example calcium hydroxide, which stops the albuminuria in the course of one and a half hours, and which probably causes a change of the disperse phase in the blood colloid, is due to the fact that proteins are amphoteric electrolytes which combine chemically with the ions of the acids and bases. The amount combined depends on the basicity of the latter at a given hydrogen ion

concentration and on the hydrogen ion concentration of the resulting solution; in other words, the combination of calcium and protein depends on whether the hydrogen ion in concentration is greater or less than that of the iso-electric point.

The statement of Rona and Takahasi [1] is interesting in regard to a possible explanation of the rôle of calcium in cases of orthostatic albuminuria or the existence of a distinction between diffusible and nondiffusible calcium ions in the blood or tissue. Their contention is of importance that the calcium content of the serums varies, but that in those cases in which it does not change, the concentration of calcium in the dialyzed serums is greater than that in the dialysate. In tetany, for instance, from 70 to 100 per cent of the total calcium was found to be diffusible in the blood serums. In 1923, Salvesan and Linder [2] found that only a decrease of ionized or nondiffusible calcium takes place in such a case. They came to the conclusion that the calcium content of the serums varies directly with its protein. These investigators have been joined by Loeb,[3] who recently issued a statement that from 25 to 40 per cent of the calcium is nondiffusible in the absence of sodium chloride, but is completely diffusible when the serums are dialyzed against a large amount of hydrochloric acid at p_H 3. This nondiffusible part of the calcium was due to the precipitation of calcium-globulate in the absence of sodium chloride at p_H 7.4. In addition to this statement, Loeb believes that the effect of pure protein and blood serums on the diffusibility of calcium finds its explanation in the Donnan theory of membrane equilibrium,[4] whereby a constant amount of sodium chloride as well as of protein and hydrogen ion concentration must be controlled, i. e., is necessary. This statement of Loeb agrees with the opinion of Kollert and Starlinger [5] that albuminuria depends on the protein concentration of the blood or the change from fine disperse to gross disperse phase of the blood colloid, which again depends mainly on its hydrogen ion concentration.

Judging the excretion of albumin, i. e., protein substance from a colloid-chemical point of view, the foregoing observations make it clear that there is a connection between diffusible and nondiffusible or

1. Rona, P., and Takahasi, D.: Biochem. Ztschr. **31**:336, 1911.

2. Salvesan and Linder: The Relation Between Calcium and Protein of Serum in Tetany Due to Parathyroidectomy, J. Biol. Chem. **58**:617 and 635, 1923-1924.

3. Loeb, R. F.: Calcium Effect of Pure Protein Solution and of Blood Serum on Diffusibility of Calcium, J. General Physiol. **8**:451, 1926. Loeb, R. F., and Nichols: Factors Influencing the Diffusibility of Calcium in Human Blood Serum, J. Biol. Chem. **72**:687, 1927.

4. Loeb and Nichols (footnote 3, second reference).

5. Kollert, V., and Starlinger, W.: Albuminuria und Blutproteines, Ztschr. f. klin. Med. **99**:426, 1924.

ionized and nonionized calcium ions. Thus, in both cases as explained in the clinical part, a decrease of ionized calcium or an ionized calcium deficiency is being dealt with, which again is supplied by the intake of liquid calcium hydroxide, whereby an equilibrium is reestablished.

As further study of the foregoing subject is in progress, I hope to present more data in the near future.

SUMMARY

Coming to a conclusion based on the results obtained with patients suffering from orthostatic albuminuria, the statement can be made that albumin is not found in the urine after the patient has fasted from the moment he gets up in the morning until noon, drinking only water, but walking and sitting up the whole forenoon, consequently being bodily active, while a positive reaction for albumin is found in cases in which the patient takes only milk or his regular meals and indulges in bodily activity. The administration of milk, however, did not cause a positive reaction during the resting hours.

The intake of lime water causes the albuminuria associated with bodily activity and the ingestion of food to cease. Its administration after each meal rendered the urine free from albumin over the period of the experiments. This suggests that a lack of calcium ions may have affected the metabolic processes of the protein substances and that the posture of persons is not the main cause of orthostatic albuminuria.

THE OCCURRENCE OF CHRONIC INTUSSUSCEPTION IN YOUNG CHILDREN *

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Probably no other symptom of childhood is more common than abdominal pain localized at, or just above, the navel. It corresponds to headache in adult life in the relative frequency of its occurrence, and often in its significance. This analogy, with some probability, is due to the fact that the chief center of the child's sympathetic nervous network lies in this location, which in early life has a more dominant rôle than at any other time. Whereas, in older patients the onset of disease is heralded by pain in the head, in children its initiation is frequently marked by pain in the abdomen. To distinguish such symptomatic pain from that significant of pathologic changes of the abdomen requires thoughtful consideration on the part of any practitioner, whether he is an internist, pediatrician or surgeon. Because of this fact, it does not seem inappropriate for me to discuss chronic intussusception, although it is a purely surgical disease, the major symptom of which is abdominal pain.

FACTS RELATIVE TO INTUSSUSCEPTION IN GENERAL

Although it may occur at any age, intussusception is primarily a disease of early life, 75 per cent of cases occurring during the first year. The vast majority are acute, but the subacute or chronic type does occur. The latter may also appear at any age, but it is seen characteristically in the second and third decades of life. Males are affected two or three times as often as females.[1] The factors involved in the production of intussusception are unknown, but it seems that the most plausible theory is the one advanced by Clubbe [2] in his excellent monograph on this subject. He expressed the opinion that while the bowel is performing its normal peristaltic movement, a constriction of the annular muscular coat occurs which may be purely local. If this constriction is greater than normal, the limit of physiologic invagination is exceeded, and the first degree of pathologic intussusception develops. If his surmise is correct, it helps to explain the predominance of this condition in infancy,

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* Read before the Rochester Pediatric Society, Annual president's address.

1. Bolling, R. W.: Surgery, New York, D. Appleton & Company, vol. 15, p. 313.

2. Clubbe, C. P. B.: Diagnosis and Treatment of Intussusception, London, Oxford University Press, 1921, p. 19.

when spasm of the intestinal musculature is most common. It also explains its not infrequent occurrence in acute enteric diseases of children. It is also possible that such a theory might explain the relative frequency of its occurrence at the site of tumors or anomalies of the intestine. Instances of this condition are frequently reported in connection with intestinal polypi, lipomas, an hypertrophied Peyers patch, an accessory pancreas, an omphalomesenteric cyst and Meckel's diverticulum.

If, then, pathologic invagination is present, what are the factors that determine whether it will be chronic or acute? It is well known that in the acute cases the obstruction is not caused by the intussusception itself, but by the edema and congestion in the wall of the bowel resulting from mesenteric traction. When the blood supply is entirely shut off, an acute intussusception occurs. If for some reason the circulation is not entirely obliterated, the invagination may continue without complete obstruction, and the condition becomes subacute; whereas, if the blood supply is not interrupted at all, it is chronic. The degree of chronicity, therefore, is determined entirely by the blood supply. When the mesentery is of average length, an acute intussusception is likely to ensue. When the mesentery is long enough to be only slightly affected or entirely unaffected by this extra load, the circulation is correspondingly unimpaired. It is in children having comparatively long mesenteries that the invagination is likely to be subacute or chronic. It further follows that this latter condition may become acute, if the blood supply is interfered with by the twisting or turning of the intussusception in any way to bring this about, which often happens following violent catharsis.

SYMPTOMS OF CHRONIC INTUSSUSCEPTION

It is unnecessary here to review the symptoms of acute intussusception, for cases that have indelibly fixed the story of this dramatic disease in mind have been seen by all pediatricians. Subacute intussusception is similar except that the patient suffers from only partial obstruction, and the symptoms are not as intense. Excellent examples of this phase of the disease are given by Bergstrom [3] in a recent article. Symptoms of the chronic form of intussusception are never typical or clearcut. Still,[4] in his usual engaging manner, described a composite case of chronic intussusception, and I quote it verbatim in place of outlining the usual symptoms.

> On a particular day the child seemed to have pain in the abdomen, and vomited once or twice. During the next few days he occasionally vomited, generally in

3. Bergstrom, V. C. A.: Subacute Intussusception, Am. J. Dis. Child. **27**: 444 (May) 1924.

4. Still, G. F.: Arch. Pediat. **38**:174, 1921.

association with a colicky pain. The vomiting has become less frequent, only once in two or three days, and the pain is only occasional. The bowels, which before were open daily, have since the onset become less regular, aperients have become necessary, and when given have worked well, and the stools have been normal; there has been no blood in the stool, or at most there has been a streak once or twice such as might be seen in the stool of any constipated child. The symptom which has most troubled the parent has been the wasting.

TWO CASES OF CHRONIC INTUSSUSCEPTION WITH REFERENCES TO OTHER CASES OF THIS DISEASE

CASE 1.—H. L., a girl, aged 3 years, from the Rochester General Hospital, had a rather stormy past history. She had had a florid eczema, many attacks of asthma and some urticaria, which developed following the ingestion of many of the staple articles of diet, such as, milk, eggs, wheat, oats or beef. She was, however, in a state of good nutrition. I was called one day to the home, and was told that for a month she had severe abdominal pain, localized at the navel, after going to bed at night. At first these pains came on two or three times a week, but when I saw her they were appearing about every other evening. I felt that probably the child was using this complaint of pain as a method of inducing her parents to allow her to stay up in the evening. A week later I was summoned again because for the preceding two hours, the child had a cramp that ceased only intermittently. At all times, the site of the pain was localized at the umbilicus. It was severe enough to cause the child to tear her skin and pull out some of her hair. I was told that since I had last seen her she had two or three attacks over a period of twenty-four hours, and that they came nearly as often during the day as during the night. There was no vomiting; the bowels moved regularly and normally; the appetite was good, and there was no fever. The abdomen could be palpated easily, but nothing abnormal could be felt; the results of the remainder of the physical examination were negative. Since I considered the case probably surgical, I asked Dr. Howard F. Prince to consult with me. He thought that he felt an object about the size of a peanut in the left flank. Laparotomy disclosed an easily reducible intussusception which involved Meckel's diverticulum. At the end of the diverticulum was a small tumor, which on microscopic examination proved to be an accessory pancreas. In all probability, this was what Dr. Prince felt on palpating the abdomen. Following the reduction of the intussusception and the removal of the diverticulum, all symptoms ceased. The patient remained free of symptoms to the time of writing, which was an interval of nine months.

The outstanding feature of this case was the attacks of cramps. The patient did not have constipation or any wasting, and in these two features she differed from the composite case described by Still. The symptoms lasted over a period of five weeks. She resembled in some particulars a case described by Owen,[5] in which the patient had neither constipation, nor abnormal stools, and who every few days had intestinal spasms with "awful agony." She differed from his patient in that there was marked loss of weight, and in the fact that his patient presented a tumor before operation. Spencer[6] reported the case of a boy,

5. Owen, A. W.: Brit. M. J. **1**:904 (May 24) 1924.
6. Spencer, F. M.: Brit. J. Surg. **8**:366 (Jan.) 1920-1921.

aged 7½ years, whose symptoms lasted over a period of four months. At the onset of his illness, he had one or two blood-streaked stools, but none after that. The first few days, his bowel movements were regular and frequent. The marked difference between this boy and the girl I have described is that in Spencer's case there was an abdominal tumor with ascites, and the diagnosis of tuberculous peritonitis had been made. Autopsy revealed the true diagnosis. Schlink [7] described the case of a girl, aged 7 years, whose symptoms of cramps and emaciation lasted over a period of two months. She had no abnormal stools. A diagnosis of sarcoma of the kidney had been made. A somewhat similar history is reported by Stone.[8] A girl, aged 2½ years, had a nine months' history of constipation and blood-streaked stools, with loss of appetite and emaciation. In her case, there was a marked tumor, and operation disclosed a sloughing intussusception. Jones [9] reported an unusual history of a girl, aged 5 years, whose abdominal pains came with defecation, although she passed normal stools. She also had a palpable mass in the abdomen. I have referred to those cases which obviously do not duplicate the case I have described, but which do confirm the universal observation that there are no pathognomonic signs of this disease, except perhaps abdominal cramps. Marsh [10] described the case of a boy, aged 2½ years, who, over a period of ten weeks, had from ten to twelve attacks of cramps daily, and occasional vomiting, and in whom no tumor was palpable. He also described a boy, aged 3 years, whose only symptom was abdominal pain over a period of ten weeks, and in whom a tumor was not felt at any time. Tumor is stated by Still as being the most characteristic feature, but this was not present in my case, nor was it present in two cases reported by Marsh.

CASE 2.—P. K., a boy, aged 5 years, had a past history that was irrelevant, except that he had had a mastoid operation a year before examination, from which he had made a good recovery. While out playing, he had been seized with a pain in the abdomen, and had run into the house. This had passed off in a few minutes, but when it recurred on the following two days, Dr. J. E. Wright, to whom I am indebted for the privilege of reporting the case, was called in. When examined the boy seemed well, and nothing was found to suggest the true state of his condition. He continued to have attacks of pain, which centered about the navel, but, in addition, he grasped the penis at such times, as if this also hurt. Finally, toward the end of the paroxysms he emitted a small amount of urine. I was asked to see the boy, and while the results of the examination of the urine were negative, I thought probably he was suffering from ureteral spasm. The

7. Schlink, H. H.: M. J. Australia **1**:270 (March 11) 1922.
8. Stone, J. S.: Boston M. & S. J. **192**:210 (Jan. 29) 1925.
9. Jones, J. G.: Brit. J. Surg. **12**:378, 1924-1925.
10. Marsh, H. E.: Ann. Surg. **79**:244, 1924.

cramps and associated penile pain became more frequent, coming on not only during the day, but during sleep as well. At no time was there any vomiting, fever or abnormal stools, except that he was constipated, or was there any appreciable loss of weight or appetite. A laparotomy was performed by Dr. Frederick W. Zimmer on the thirteenth day of the boy's illness. An easily reducible intussusception of the ascending colon was found. He was followed for six months by Dr. Wright, at the end of which time he moved out of town, but during the period of observation, he was free from any trouble.

I can find only four cases which simulate this boy's history, and these do not exactly duplicate it. Stallman,[11] described the case of a boy who had abdominal pain with urinary frequency. Waugh [12] reported three boys who had penile pain during the paroxysms, but did not always emit urine, as my patient did. Incidentally he could not feel a tumor in one of his boys. In the other two, however, it was present. In commenting on this particular symptom of chronic intussusception, Waugh ventured the theory that it is due either to the direct pull of the abdominal mesocolon on the kidney with traction on the nerves or perhaps to the weight of the intestine on the kidney itself. It seems to me that the first is more plausible, since in one of his cases, and in my case, there was a distinct suppression of urine, the children passing only a few ounces a day, despite a fairly normal intake of fluid.

DIFFERENTIAL DIAGNOSIS OF CHRONIC INTUSSUSCEPTION

While it is the general observation that the condition in these patients is diagnosed at operation, it should not always be impossible to make a correct interpretation of the presenting symptoms. The differentiation of chronic from recurrent intussusception is not difficult. Children with the recurrent form have recurrent attacks, often months apart, of typical acute intussusception. Such a case is reported by Kelloch.[13] The child he described had five attacks over a period of thirteen months. To distinguish this disease from tuberculous peritonitis, however, is more difficult. Here there are abdominal pain, wasting, constipation and the appearance of a tumor, which may indeed simulate the tumor of an intussusception. In general, the intracutaneous test would be of value; also a knowledge of the type of abdominal pain. It is not as severe and not productive of violent cramps. The tumor also possesses characteristics which help the pediatrician. When the tumor of intussusception is palpated, one can feel the waves of contraction due to intestinal peristalsis. This is a point emphasized by Still. In the tumor found in tuberculous peritonitis, no such motion is apparent. Chronic peritonitis due to the pneumococcus may give symptoms almost

11. Stallman, J. F. H.: Ann. Surg. **84**:735, 1926.
12. Waugh, G. E.: Lancet **1**:1492 (June 3) 1911.
13. Kelloch, T. H.: Lancet **2**:154 (July 20) 1912.

identical with those in chronic intussusception. But in this disease, as I have pointed out in a paper on that subject,[14] there is usually a previous empyema or acute pneumococcic peritonitis, which has become localized and chronic by the formation of adhesions. Recently, I saw a boy whose abdomen had been run over by an automobile. Over a period of a month, he had intermittent and intense abdominal pain. There was vomiting, but no fever. Laparotomy disclosed a colon peritonitis. His abdomen was bloated and the umbilicus was pouting, which are conditions rarely encountered in chronic intussusception.

I recently reported two cases of lymphoid hyperplasia of the appendix.[15] The patients had histories almost indistinguishable from that in the disease under discussion. However, the cramps were not so severe, and there was no tumor. Lymphoid hyperplasia of the mesenteric glands gives many similar symptoms, but in this disease the abdomen is nearly always tender, which is rarely the case in chronic intussusception. Lead poisoning might give these severe intestinal paroxysms, but here one can rely on the history of exposure, the lead line on the gums or the stippling of the red blood cells. Some reported cases had been diagnosed as sarcoma of the kidney or of the sigmoid, but in these cases intestinal pain is rare and Still's sign is absent. Symptoms which might be due to stone in the ureter or bladder or infection of the urinary tract were present in one of my four cases, and four instances were found reported in the literature. It seems to me that diagnosis here must rest on the finding of a typical tumor, or at least definite proof that the child's kidney and bladder are normal.

SUMMARY

Judging from the number of cases reported, chronic intussusception is an extremely rare disease in children, but its occurrence may not be as infrequent as this fact would lead one to believe. Its symptoms are practically never characteristic, and it may be that children have been allowed to die from this condition because of a faulty diagnosis. Two cases are reported and a brief review of the literature is presented. The purpose of this paper is to call enough attention to the presence of this condition so that anyone observing severe abdominal pain, which is localized at the navel, may at least have this disease in mind.

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14. Beaven, P. W.: Pneumococcus Peritonitis in Infancy and Early Childhood, Am. J. Dis. Child. **20**:341 (Oct.) 1920.

15. Beaven, P. W.: Lymphoid Appendicitus, Am. J. Dis. Child. **35**:541 (March) 1928.

Progress in Pediatrics

THE VITAMIN CONTENT OF MILK USED IN INFANT FEEDING*

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DETROIT

During the past four years, comparative studies on the vitamin content of human milk and cow's milk have been in progress in these laboratories.[1] A summary of the results obtained are herewith presented for the purpose of aiding those charged with the care of infants in evaluating the two types of milk so frequently used interchangeably in infant feeding. These data, together with their discussion, may be of value in establishing a more adequate understanding of the growth-promoting and disease-protecting requirements of infants, and in explaining some of the causes and conditions of malnutrition in infants.

At present the vitamin content of foods is given in terms of the volume or weight of a given substance required to produce growth and to protect against or cure a specific vitamin deficiency disease in standard experimental animals held under carefully controlled conditions. Thus, the quantitative aspect of the vitamins can be discussed only from the standpoint of their content in, not percentage of, a food.

Raw untreated human milk and cow's milk were used in these studies. The breast milk obtained from the Mother's Milk Bureau of Detroit represented an aliquot portion of fresh pooled milk from approximately a dozen wetnurses in various stages of lactation, who expressed their milk aseptically into sterile bottles which were immediately sealed airtight and chilled. No attempt was made to control the diets, in either quality or quantity, since it was desired to study the milk secreted by

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1. Macy, I. G.; Outhouse, J.; Graham, A., and Long, M. L.: Human Milk Studies: II. The Quantitative Estimation of Vitamin A, J. Biol. Chem. **73**:175 (May) 1927; Human Milk Studies: III. The Quantitative Estimation of Vitamin B, ibid. **73**:189 (May) 1927. Outhouse, J.; Macy, I. G.; Brekke, Viola; and Graham, A.: Human Milk Studies: IV. A Note on the Vitamin A and B Content of Cow's Milk, ibid. **73**:203 (May) 1927. Outhouse, J.; Macy, I. G., and Brekke, Viola: Human Milk Studies: V. A Quantitative Comparison of the Antirachitic Factor in Human Milk and Cow's Milk, ibid. **78**:129 (June) 1928.

women observing the usual American dietary. The fat content of the pooled milk fluctuated between 2.7 and 3.5 per cent. A standard quality of milk is maintained by the Mother's Milk Bureau by accepting milk from only those women whose own infants are in good nutritive condition, and by rejecting milk which consistently shows abnormal variations in its content of fat, total protein, total solids and other matter. The Walker-Gordon certified cow's milk was produced by a herd of 450 Holstein cows held under the best of hygienic and nutritive conditions. The fat content of the milk approximated 3.8 per cent.[2]

For the vitamin-testing of these milks, rats have been employed. Advantage has been taken of the newer biologic technic which reduces to a minimum the variability in the test animals. By rearing rats under standardized conditions, it is possible to predict with accuracy their deportment on various dietetic regimes. Thus, when a rat is placed on a ration containing protein, carbohydrate, minerals and all the known essentials vitamins, normal growth ensues and sexual maturity occurs early, and the females are able to reproduce and to nurse their litters successfully. On the other hand, when a specific vitamin is withheld, nutritional failure results; this is manifested by symptoms which are also characteristic to man.

THE VITAMIN A CONTENT OF HUMAN MILK AND OF COW'S MILK

When these experiments were begun, cow's milk had been investigated considerably for its vitamin A content, whereas only few observations had been made on human milk.

In 1922, Kennedy and Dutcher[3] found that the daily administration of 10 cc. of a good grade of summer cow's milk was necessary to supply the vitamin A needs of young rats. Three years later, Kennedy, Palmer and Schlutz[4] reported the first studies on vitamin A on human milk, making the significant observation that this factor in mother's milk depended on its presence in her diet. Thus the vitamin A requirement of rats was met by 10 cc. of milk when the dietary of the woman was well balanced, but not when the intake of food was grossly inadequate. In all of these experiments, however, vitamin A was not the only variable, and when Honeywell and Dutcher[5] supplemented the rat's diet with the antirachitic factor, they obtained good growth with as little as 2 cc. of cow's

2. Study of antiscorbutic content of milks has been omitted. This has seemed to be of minor importance in view of the fact that it is universally recognized that vitamin C adjuvants must be added.

3. Kennedy, C., and Dutcher, R. A.: Vitamine Studies: IX. The Influence of the Diet of the Cow Upon the Quantity of Vitamines A and B in the Milk, J. Biol. Chem. **50**:339 (Feb.) 1922.

4. Kennedy, C.; Palmer, L. S., and Schlutz, F. W.: Vitamin Content of Breast Milk, Tr. Am. Pediat. Soc. **35**:26, 1923.

5. Honeywell, H., and Dutcher, R. A.: Feeding Technique in the Study of Vitamin A, Proc. Am. Chem. Soc., Philadelphia, 1926.

milk daily. Recently, Platon[6] reported that 2 Gm. of whole milk was sufficient, whereas 20 Gm. of the skimmed milk was insufficient to produce normal growth in the rat. Hart[7] expressed the opinion that approximately 90 per cent of the vitamin A is removed by the skimming process.

In the studies on vitamin A, when the standardized rats were maintained on a vitamin A-free diet, they grew normally for approximately five weeks. By this time the vitamin A stored in their bodies had become exhausted, this condition being heralded by infections of the respiratory tract, cessation of growth and the appearance of xerophthalmia. It was at this point that whole raw human milk and cow's milk were introduced into the diet.

Quantities of from 2.5 to 3 cc. daily of either kind of milk were sufficient to cure animals that had xerophthalmia and to allow for restoration of growth, thus demonstrating that both types contain approximately the same amount of vitamin A. In other experiments, when the storage depots of vitamin A were not first exhausted from the body, it was possible to secure the same rate of growth with a smaller quantity of milk, the amount of a specific adjuvant being apparently greater for therapeutic purposes than for prevention. Involvement of the mastoid cells was a general observation at autopsy when animals had been held for an extensive period on minimum levels of vitamin A, although their nutritive condition appeared good.

The efficacy of a particular food has not been judged only by its ability to alleviate symptoms and to reinstate growth. Special consideration has been given to the periods of greatest metabolic activity in order to portray more accurately the effect of minimum quantities of a specific substance over a long period of time, as may be true of human dietaries. These female rats, therefore, growing at an accepted rate on the minimum amounts of milk, were bred; observations were made, not only on the deportment of the rats during gestation and lactation, but particularly on the deportment of their young. Reproduction was found to be normal, and lactation was satisfactory from the standpoint of the maternal organism. At the end of the lactation period, the mothers were in good physical condition, and appeared well nourished, healthy and active.

The apparently normal young when transferred to the vitamin A-free diet revealed a limited body storage of vitamin A. Instead of the usual thirty-five days elapsing before their storage supply of this factor was exhausted, some of the rats ceased growing at once; others died within a few days without exhibiting characteristic symptoms; the majority, however, made poor gains in weight and developed xerophthalmia as early

6. Platon, J. B.: Der A-Vitamingehalt der Magermilch, Biochem. Zchnschr. **185**:238, 1927.

7. Hart, E. B., in McCollum, E. V., and Simmonds, N.: Newer Knowledge of Nutrition, ed. 3, New York, The Macmillan Company, 1925, p. 156.

as from the sixth to the twelfth day. Autopsy observation of these rats showed generalized abscesses with yellow purulent material in the upper respiratory and digestive tracts involving the glands at the base of the tongue, the soft palate and the salivary glands. In every instance, this pus-like material was found in the middle ear or in the mastoid. A consistent observation was the marked atrophic condition of the salivary and pancreatic tissue with an apparent loss of function. There was also a marked anemic condition of the lungs, liver, kidneys and mucous membranes, denoting poor utilization of the iron of the diet. The advanced degree to which these gross pathologic lesions had progressed within so short a period of time indicates that these changes must have begun during the suckling period.

Mori,[8] Wolbach and Howe,[9] Goldblatt and Benischek,[10] studying the cause of death in animals on vitamin A-low or deficient diets, found that the primary microscopic observation is that of a metaplasia of the cylindric, cuboidal and transitional cells of the epitheliums to the squamous keritanizing type. The organs involved were the trachea, large and small bronchi in the lung, posterior nares, accessory salivary glands of the base of the tongue, para-ocular, submaxillary, sublingual and parotid glands, the renal pelvis, the ureter and the bladder. In confirmation of the observations of Daniels, Armstrong, and Hutton [11] and of Sherman and Munsell,[12] they found abscesses or cysts consistently in the base of the tongue and occasionally in the submaxillary glands, and when an inflammatory process was present, it occurred coincident with or subsequent to the metaplasia and was not responsible for the initiation of the changes. Goldblatt and Benischek [10] described these cysts as "lined completely, or in part, by squamous epithelium, filled with keratohyaline material." These profound tissue changes have their counterpart in the human species, as shown by Wilson and DuBois [13] in their detailed autopsy report of xerophthalmia in an infant.

Investigators of nutrition who use the rat as an experimental animal in vitamin A studies agree that the first symptom of deficiency disease

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8. Mori, M.: Ueber die sogenannte Hikan (Xerosis conjunctivae infantum ev Keratomalacie), Jahrb. f. Kinderh. **54**:175, 1904.

9. Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble Vitamin, J. Exper. Med. **42**:753, 1925.

10. Goldblatt, H., and Benischek, M.: Vitamin A Deficiency and Metaplasia, J. Exper. Med. **46**:699 (Nov.) 1927.

11. Daniels, A. L.; Armstrong, M. E., and Hutton, M. K.: Nasal Sinusitis Produced by Diets Deficient in Vitamin A, J. A. M. A. **81**:828 (Sept. 8) 1923.

12. Sherman, H. C., and Munsell, H. E.: The Quantitative Determination of Vitamin A, J. Am. Chem. Soc. **47**:1639, 1925.

13. Wilson, J. R., and DuBois, R. O.: Report of a Fatal Case of Keratomalacia in an Infant, with Post-Mortem Examination, Am. J. Dis. Child. **26**:431 (Oct.) 1923.

is an infection of the upper respiratory tract. This may be evidenced by snuffles, labored breathing, nasal hemorrhages and infections of the lung. In 1923, Daniels and her associates,[11] dissecting the skulls of rats that had suffered from a deficiency of vitamin A, observed "that in all cases paranasal sinuses and the mastoid cells contained purulent material." Dean,[14] while making observations on diseases of the paranasal sinus in infants and children, noted a similarity in these symptoms experimentally produced in rats by Daniels. It was found that these symptoms in both rats and infants were alleviated by the generous feeding of vitamin A. The observation of a purulent discharge from the nose is in accord with that of Ross[15] who observed the same condition in infants suffering from xerophthalmia. In his cases of xerophthalmia in children, Bloch[16] observed a simple catarrhal infection of the mucous membrane, particularly of the respiratory organs and the middle ear. He is of the opinion that if children with xerophthalmia do not die with a secondary infection, the most frequent cause of death is bronchopneumonia. Daniels[11] stated that "the fat-soluble A plays an important rôle in the immunity of the organ to pyogenic infections." Cramer[17] expressed the belief that one of the most constant effects of a diet deficient in vitamin A is the development of bacterial infection of an avirulent type.

In rats, changes in the tissues of the eye occur at about the time when growth ceases. In Bloch's[16] opinion, the initial change in children is the production of night-blindness or hemeralopia. According to McCollum,[18] this inability to see in subdued light may be found in various parts of the world among peoples whose dietaries are habitually low in fat. The experimental proof of this has been advanced by Fridericia and Holm,[19] who produced hemeralopia in rats by dietaries deficient in

14. Dean, L. W.: Paranasal Sinus Disease in Infants and Children, J. A. M. A. **85**:317 (Aug. 1) 1925.

15. Ross, S. G.: Nutritional Keratomalacia in Infants, Am. J. Dis. Child. **22**:232 (Sept.) 1921.

16. Bloch, C. E.: Blindness and Other Diseases in Children Arising from Deficiency Nutrition (Lack of Fat Soluble A Factor), Am. J. Dis. Child. **27**:139 (Feb.) 1924; Further Clinical Investigations Into the Disease Arising in Consequence of a Deficiency in the Fat-Soluble A Factor, ibid. **28**:659 (Dec.) 1924.

17. Cramer, W., and Kinsbury, A. N.: Local and General Defenses Against Infections, and the Effect on Them of Vitamin-Deficiency, Brit. J. Exper. Path. **5**:300 (Oct.) 1924.

18. McCollum, E. V., and Simmonds, Nina: Newer Knowledge of Nutrition, ed. 3, New York, The Macmillan Company, 1925, p. 289.

19. Fridericia, L. S., and Holm, E.: Experimental Contribution to the Study of the Relation of Night Blindness and Malnutrition: Influence of Deficiency of Fat-Soluble A Vitamin in the Diet on the Visual Purple in the Eyes of Rats, Am. J. Physiol. **73**:63 (June) 1925.

vitamin A. Bloch [16] found that simultaneous with hemeralopia, there is a dryness of ocular conjunctiva (xerosis) and that:

> The dryness extends over the cornea, which becomes hazy, shrivels up and shortly after pieces of it become necrosed. In most cases the ocular conjunctiva is injected, the child then has photophobia, the conjunctiva is red and swollen, and the eyes begin to water. When the cornea necroses the inflammation spreads to the interior of the eye. The inflammation may be so intense and widespread in many cases that it almost obscures the original xerosis. . . . If the disease is not recognized in time, the child becomes blind.

In reading case reports of children suffering from a deficiency of vitamin A, one finds the early appearance of gastro-intestinal symptoms in the form of acute intestinal indigestion with diarrhea, the stools being greenish and slimy and without blood. This condition has its counterpart in kittens fed diets low in vitamin A.[20] The kittens in these experiments developed abdominal distention and diarrhea, and post mortem the walls of the intestines were thin, much like those of children suffering from celiac disease. As numerous investigators [21] have observed the occurrence of infections of the oral and nasal passages, together with acute intestinal disorders, the presence of these two symptoms should lead to an investigation of the dietary in respect to its content of vitamin A.

The development of calculi in the urinary tract of animals on vitamin A-low diets was noted by Osborne and Mendel.[22] These observations were verified by Fujimaki,[23] and more recently by van Leersum [24] who demonstrated calcium deposits not only in the urinary tract but also in the kidney tubules of rats on a diet deficient in vitamin A for a period of from thirteen to fifty-four days. In our experiments, calculi have been found frequently in the gall ducts of rats kept for a long time on rations low in vitamin A.

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20. MacKay, H. M. M.: The Effect on Kittens of a Diet Deficient in Animal Fat, Biochem. J. **15**:19, 1921.

21. Lyman, H. W.: Mastoiditis, a Cause of Gastro-Intestinal Disturbance in Infants, J. Missouri M. A. **22**:293 (Aug.) 1925. Hartman, A. F.: Chemical Changes Occurring in the Body as the Result of Certain Diseases: I. The Effects of Diarrhea, Vomiting, Dehydration and Oliguria on the Acid-Base Balance of the Plasma of Infants with Mastoiditis, Am. J. Dis. Child. **35**:557 (April) 1928.

22. Osborne, T. B., and Mendel, L. B.: The Incidence of Phosphatic Urinary Calculi in Rats Fed on Experimental Rations, J. A. M. A. **69**:32 (July 7) 1917.

23. Fujimaki, Y.: Formation of Urinary and Bile Duct in Animals Fed Experimental Rations, Japan M. World **6**:29, 1926; abstr., Chem. Abstr. **20**:2694, 1926.

24. Van Leersum, E. C.: Vitamin A Deficiency and Urolithiasis, J. Biol. Chem. **76**:137, 1928.

Changes in the blood also occur when underfeeding with vitamin A occurs. Koessler, Maurer and Loughlin [25] produced anemia in rats; the blood picture was identical in all respects to that in pernicious anemia. They were able to correct the condition by feeding diets rich in vitamin A. They stated that blood regeneration cannot take place in the absence of this vitamin. Cramer [26] stated that thrombopenia is a constant symptom of vitamin A insufficiency. A possible relationship may exist between vitamin A deficiency and primary purpura, since thrombopenia and gastro-intestinal disturbance are characteristic symptoms of both. One of the patients in the cases cited by Ross [15] came to him with a diagnosis of purpura and keratomalacia; in another case, numerous petechiae were visible on the abdominal wall. Schwartz [27] noted a similar condition in the case reported by him.

Certain neurologic symptoms were observed in animals kept for a long period of time on vitamin A-low dietaries. We [28] observed in the fore legs of our rats a disturbance in motor function which suggested incoordination or partial paralysis. Hughes,[29] retaining pigs for a year or more on a food mixture low in vitamin A, demonstrated histologically a degeneration of nervous tissue. Schwartz,[27] reviewing clinical literature, found manifestations of nervous symptoms occurring in cases of xerophthalmia. Hyperirritability, opisthotonos and rigidity of the neck were frequently encountered.

COMMENT

The experimental and clinical demonstrations of the untoward effects of dietaries low or deficient in vitamin A emphasizes the necessity of examining critically, not only the food of the infant, but also the maternal diet during the periods of fetal and infant dependency. In view of the fact that in the United States one may be dealing with dietaries not wholly devoid of vitamin A, one may not be confronted with the gross pathologic process of xerophthalmia, but rather with borderline conditions such as anorexia, cessation of growth, gastro-intestinal disturbances and susceptibility to infection of the nasal sinus, middle ear

25. Koessler, K. K.; Maurer, S., and Loughlin, R.: The Relation of Anemia, Primary and Secondary, to Vitamin Deficiency, J. A. M. A. **87**:476 (Aug. 14) 1926.

26. Cramer, W.: On the Mode of Action of Vitamins, Lancet **1**:1046 (May 26) 1923.

27. Schwartz, A. B.: Nutritional Keratomalacia, J. A. M. A. **85**:2025 (Dec.) 1925.

28. Macy; Outhouse; Graham and Long (footnote 1, first reference).

29. Hughes, J. S., and Leinhardt, H. S.: Nerve Degeneration Resulting from Avitaminosis A in Pigs, Paper read before the Annual Meeting of the American Chemical Society, St. Louis, April 16-20, 1928.

and mastoid. In the absence of well defined physical or bacterial causes, such symptoms may be significant of an appreciable deficiency of vitamin A in the diet.

The reaction of the infant to diets containing subminimal amounts of vitamin A depends wholly on the amount of this substance that has been stored in its tissues in utero and during the nursing period. If its pabulum has been rich in vitamin A, the organism has been able to store a certain amount for subsequent times of need. If, on the other hand, the food meets only the immediate requirement of the infant, storage cannot take place, and therefore in a period of low vitamin A consumption, a nutritional breakdown may occur within a few days. This is the obvious explanation of the case reported by Schwartz [27] in which advanced xerophthalmia developed within twenty-one days on an inadequate artificial diet, although the infant had previously been breast fed for ten months. The analogue in rats has been seen in the animals in which from 2 to 3 cc. of human milk was received daily by the mothers as the only source of vitamin A throughout growth, gestation and lactation.

Bloch [16] never observed a case of xerophthalmia in an infant whose mother was capable of producing a sufficient quantity of milk. It has been demonstrated experimentally in the dairy industry that vitamins appear in the milk only as they are present in the food; that is, the animal body cannot synthesize these organic complexes. As previously cited in this paper, Kennedy, Palmer and Schlutz [4] found a direct relation between the diet of the human mother and the vitamin content of her milk. It is therefore necessary that the diet of the nursing mother should contain an abundance of vitamin A, this being important not only for her own well-being, but especially for that of her offspring.

The amount of vitamin A absorbed depends not only on the availability, but also on the utilizability, of this substance by the organism. We have shown that both whole human milk and cow's milk contain approximately the same amount of vitamin A. Daniels,[30] however, showed that the vitamin A in the food of the breast-fed baby is more completely absorbed than is that of cow's milk mixtures. Her experiments indicate that a portion of the vitamin A in cow's milk may be carried through the intestinal tract along with the calcium soap of the stools. In cases of debilitation and atrophy of the intestinal mucosa, utilization of food nutrients may not be complete. This is particularly true in diarrheal conditions. The derangement of the organs secreting digestive juices, namely, the salivary glands and the pancreas, as found in vitamin A deficiency, may also be responsible for a diminished utiliza-

30. Daniels, A. L.: Vitamin A Content of Fecal Excretion of a Breast Fed and Artificially Fed Infant, Proc. Soc. Exper. Biol. & Med., **23**:824, 1926.

tion. Bloch,[16] recognizing this, emphasized the contributory rôle of impaired digestion in the genesis of xerophthalmia.

When cow's milk is substituted for breast milk, precaution must be taken to maintain the original vitamin A value. Skimmed milk formulas contain a paucity of this dietary essential, since the greater portion resides in the fat moiety. In this respect, it is of interest to recall that Bloch found xerophthalmia in children fed on formulas of skimmed milk and butter-milk or on diets low in fats. Vitamin A readily undergoes deterioration through oxidation by drying, through repeated heating or heating at a high temperature for a long period of time in the presence of air and also by ageing. Thus in the process of the preparation of proprietary infant foods, the vitamin A content may be partly destroyed. In the cases of xerophthalmia in children observed by Ross,[15] condensed milk had served as the diet for a considerable period of time.

The vitamin A needs of an infant depend on the maternal dietary during gestation and lactation, on age and on proper functioning of the gastro-intestinal tract. In the interchange of cow's milk for breast milk, consideration must be given to the possibility of the vitamin A dissipation through oxidation prior to or during the preparation of the formula, through the use of milk from which a portion of the fat has been removed and through the occlusion in the fatty acid soaps in the intestinal tract. Adjuvants rich in vitamin A, therefore, should be added early to the diet of the breast-fed as well as of the artificially fed infant. This would not only protect against a widespread series of pathologic changes, but would aid particularly in the promotion of optimal well-being.

THE VITAMIN B CONTENT OF HUMAN MILK AND COW'S MILK

The first direct comparison of the antineuritic properties of cow's milk and human milk was made in 1913 by Gibson,[31] who, judging from his own experiments in feeding cow's milk to fowls and from the results of others, suggested that normal human milk could contain only about one-fourth the amount of vitamin B found in cow's milk. In 1918, Osborne and Mendel,[32] using rats as experimental animals under carefully controlled conditions, found that there was no evidence of a greater content of vitamin B in human milk than in cow's milk. More recently, Kennedy and his associates [4] found that whereas 10 cc. of cow's milk daily was sufficient to support growth in rats on diets that were adequate except in the vitamin B content, an equivalent amount of human milk was insufficient. With the information at hand, we are unable to

31. Gibson, R. B.: The Protective Power of Normal Human Milk Against Polyneuritis Gallinarum (Beriberi), Philippine J. Sc. **8**:469, 1913.

32. Osborne, T. B., and Mendel, L. B.: Carnegie Inst. of Washington Year Book **19**:3819, 1920.

interpret the conflicting results reported by Suzuki [33] in Japan, who found that from 2 to 3 cc. of a poor grade of human milk protected rats against polyneuritis.

In these laboratories, the comparison of the vitamin B content of human milk and of cow's milk has been repeated. Standardized technic has been used and the experiments have been extended by the feeding of both types of milk in quantities sufficient to produce normal growth over a long period of time, thus creating dietary conditions more comparable to human experiences.

Young rats with the same nutritional and environmental history as described previously[34] were placed on the experimental vitamin B-free ration on the twenty-first day of life. As under certain dietetic conditions excreta may contain some vitamin B, the animals were placed on false bottom trays to prevent coprophagy. Growth ceased quickly, indicating that vitamin B, in contrast to vitamin A, cannot be stored in animal tissues to any appreciable extent. Coincident with cessation of growth there is a loss in appetite; decline in weight progresses until the animals become emaciated; priapism is frequent, and food intake is reduced to a minimum. If maintained on this experimental diet, the majority of the animals die before the fourth week; those that survive develop muscle incoordination, loss of equilibrium and paralysis; death is the inevitable result. The procedure followed has been to feed the vitamin B adjuvant as early as the tenth to the fourteenth day before the vitality of the rat has been impaired to any appreciable extent by pathologic changes.

To these rats retarded in development, quantities of from 5 to 35 cc. of human milk have been fed daily, as the source of vitamin B, apart from the basal ration. Fair growth was reinstated by 16, 18 and 20 cc. Sexual maturity, however, was indefinitely postponed with amounts below 18 cc., and the normal four to five day estrous cycle took place with a minimum of 20 cc. Normal growth was obtained in the majority of cases when successively 20, 25, 30 and 35 cc. of human milk were given daily, thus demonstrating an increased demand for vitamin B accompanying increase in body weight. When cow's milk was fed under the same conditions, a normal increment in weight was stimulated for four weeks by 12 cc. daily, for eight weeks by 16 cc. and for twelve to sixteen weeks by either 20 or 25 cc. Growth, although within normal limits in animals fed 30 and 35 cc. of human milk daily, was not as satisfactory as that obtained by feeding 20 cc. of cow's milk. In addi-

33. Suzuki, T.: Studies in the Vitamin B Content in Mother's Milk of Infants Suffering from Infant Beriberi, Orient. J. Dis. Inf. **1**:51, 1926.

34. Macy, I. G.; Outhouse, J.; Long, M. L., and Graham, A.: Human Milk Studies: I. Technique Employed in Vitamin Studies, J. Biol. Chem. **73**:153 (May) 1927.

tion, the behavior of rats on rations of human milk was not consistently uniform, probably due to lowered consumption of basal food and to the persistent diarrheal condition accompanying the ingestion of 14 cc. and more of human milk.

With the experimental proof that the so-called vitamin B consists of two fractions, these experiments were extended, the thermolabile and thermostable components being fed to rats that had ceased growing on large quantities of human milk or cow's milk. When both fractions were given in the form of the brewer's yeast, further growth was obtained in both series. When autoclaved yeast, containing the thermostable fraction, was fed in conjunction with cow's milk, there was no response in growth, whereas with human milk resumption of growth resulted. Thus it would appear that cow's milk contains more of the pellagra-preventive than of the antineuritic fraction, and vice versa for human milk.

The quantities of human milk sufficient to produce normal ovulation in rats were also adequate to meet the vitamin B requirement for reproduction but not for lactation. When 25, 30 and 35 cc. were fed daily, the rats cast litters normal in size and appearance. Lactation, however, was uniformly unsuccessful as judged by the deportment of both the mother and her young. By the seventh day, the young were subnormal in weight, appearance and behavior; the skin was dry and wrinkled, and the hair developed slowly, giving an unkempt appearance; they were unusually nervous and restless. Throughout the lactation period the mothers progressively lost weight, ate less food and frequently ate their young. When their diet was supplemented further with yeast, their weight and appetite increased; simultaneously, improved growth of the young occurred with rapid disappearance of the nervous symptoms. For the successful rearing of young, we have found that the vitamin B requirement of the mother is four to five times in excess of her growth needs.

These experiments indicated that cow's milk is slightly superior to human milk in its vitamin B content. Demonstration has been given, too, of the fact that a mother rat cannot successfully rear young on the diet containing vitamin B in amounts sufficient only for growth and maintenance of weight.

In its symptomatology, mode of production and cure, polyneuritis in these animals is analogous to the beriberi in man which results from prolonged subsistence on dietaries limited in vitamin B. Andrew,[35] discussing this disease in infants, stated that the presence of edema may frequently so mask the disease that the infants seem plump and apparently well nourished. There is an insidious appearance of such symptoms as cyanosis around the mouth and nose, slight dyspnea, periodic

35. Andrew, V. L.: Infantile Beriberi, Phillipine J. Sc. **7**:67 (April) 1912.

restlessness, insomnia, occasional vomiting, digestive disturbances and increased pulse rate. In general, the constant observations in beriberi, either the dry or wet form, are retardation in growth or loss in weight, anorexia, gastro-intestinal disturbances, muscle atrophy and peripheral neuritis. Observations at autopsy show dilatation and hypertrophy of the right side of the heart, and hemorrhage of the serous membrane of the stomach and duodenum and degeneration of the nerves.

In the experimental laboratory, one of the first changes observed in animals maintained on a vitamin B-free diet is a retardation of growth and loss in weight. In 1918, Osborne and Mendel [36] demonstrated a quantitative relationship between body weight and vitamin B requirements, observations that have since been confirmed on several species. Thus, the rate of growth of an animal may be regulated within certain limits by the quantity of vitamin B in the diet, and retardation in growth or loss in weight follow as a consequence of subminimal consumption of this substance. Significant confirmatory evidence is presented in the studies on milk herewith reported which show that growth ensued only when the daily quantities of milk were increased proportionally to the gain in weight or size of the animal.

The loss in body weight induced by prolonged retention on dietaries low in vitamin B is accompanied by a lack of desire for food which may lead progressively to total abstinence. In experimental animals, anorexia may appear within a few days when there is a paucity of this factor in the diet. Thus, in 1920, Karr [37] was led to conclude that there was some relation between the desire for food and the amount of vitamin B ingested. Later Cowgill, Deuel and Smith [38] demonstrated a quantitative relationship. They found that substances promoting normal growth in rats would likewise maintain appetite in the dog. Further evidence of control of appetite, as well as of growth by vitamin B is given in the immediate recurrence of appetite and resumption of growth when this substance is fed in adequate quantities. This rapid and striking response in the desire for food has led Smith [39] to believe from her experiments that vitamin B-deficiency causes pseudoanorexia rather than true anorexia.

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36. Osborne, T. B., and Mendel, L. B.: The Rôle of Vitamin B in Relation to the Size of Growing Rats, J. Biol. Chem. **63**:233 (March) 1925.

37. Karr, W. G.: Some Effects of Water-Soluble Vitamine Upon Nutrition, J. Biol. Chem. **44**:255 (Nov.) 1920.

38. Cowgill, G. R.; Deuel, H. J., and Smith, A. H.: Studies in the Physiology of Vitamins: III. Quantitative Aspects of the Relation Between Vitamin B and Appetite in the Dog, Am. J. Physiol. **73**:106 (June) 1925.

39. Smith, E. A.: Gastric Motility in Vitamin B Deficiency in the Dog, Am. J. Physiol. **80**:485 (May) 1927.

The gastro-intestinal disturbances accompanying the disease present a varied picture. Constipation, as a general observation in beriberi, has been observed particularly by Andrew [35] in children, by Hoffman [40] in Chinese women, by Moore and Brodie,[41] Drummond and Marrian,[42] and Plimmer and his associates [43] in rats. Such observations may be explained by the statement of McCarrison [44] that there is a marked impairment of the neuromuscular control of the intestine with consequent failure of the contents to be transported in a normal manner. Cowgill and his co-workers,[38] while studying dogs on vitamin B-free diets, noticed a gradually developing gastric atony. Pathologic changes in the intestinal tract have been noted. McCarrison stated that in polyneuritis in monkeys and in pigeons there is complete atrophy of the villi of the stomach and of the glandular cells of the crypts of Lieberkühn. Manson,[45] who was thoroughly conversant with beriberi, believed that "the only lesion that might be considered specific in beriberi is the duodenitis which may be present in acute cases during the first three weeks of the disease." Such behavior of the gastro-intestinal tract may partly explain the results obtained by Farmer and Redenbaugh,[46] who found a marked decrease in the digestion of starch, protein and fat, owing to a failure in either the secretion or the activation of the digestive enzymes.

Vomiting is one of the late symptoms in polyneuritis. Cowgill and his associates [38] found it occurring constantly prior to convulsions in dogs. Smith [39] considered vomiting a sequence of the extreme nervous disorder, and Manson [45] believed it an indication of involvement of the pneumogastric nerve. The latter investigator regarded vomiting as an ugly and threatening symptom in beriberi, and stated that the Japanese consider its occurrence as of fatal consequence.

The muscular system suffers marked degenerative and atrophic changes in vitamin B deficiency disease. Before paralysis and convulsions occur, muscular weakness may be evident. In rats this takes the

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40. Hoffman, J. D.: Beriberi in Chinese Women and Its Relation to Child Bearing, China M. J. **38**:987, 1924.

41. Moore, C. U., and Brodie, J. L.: The Relation of Maternal Diet to Hemorrhage in the New-Born, Am. J. Dis. Child. **34**:53 (July) 1927.

42. Drummond, J. C., and Marrian, G. F.: The Physiological Rôle of Vitamin B: I. The Relation of Vitamin B to Tissue Oxidation, Biochem. J. **20**:1229, 1926.

43. Plimmer, R. H. A.; Rosedale, J. L., and Raymond, W. H.: Experiments on Nutrition: VI. Balance of Food by Vitamin B, Biochem. J. **21**:913, 1927.

44. McCarrison, R.: Studies in Deficiency Disease, London, Oxford University Press, 1921.

45. Manson, P. H.: Manson's Tropical Diseases, ed. 7, New York, 1923.

46. Farmer, C. J., and Redenbaugh, H. E.: The Decrease in Digestive Efficiency in Polyneuritis Columbarum, Am. J. Physiol. **75**:45 (Dec.) 1925.

form of extreme unwillingness to exercise. Nelson and his co-workers,[47] noticing this, found that excised rat muscles showed a progressive diminution in amplitude, endurance and tonicity as the length of time on the diet progressed. In discussing the disease in the human species, Manson remarked about the emaciated, flabby and painful condition of the muscles of the extremities, and that their reaction to electrical stimulation was typical of degenerative changes. Cowgill and his associates [48] expressed the belief that neuritic symptoms, such as convulsions and spastic paralysis in the dog, are due to an accumulation of toxic substances in the muscles. Other evidences of muscular change are the loss of the swallowing reflex of pigeons, the condition of priapism in rats and such changes as are found at autopsies on beriberi patients; i.e., dilatation of the heart and arterial system.

The part that the nervous system plays in causing convulsions in polyneuritis of man and animals is not adequately explained. Hofmeister [49] was unable to find degeneration of the nerve cell in beriberic rats, and Cowgill did not find it in his polyneuritic dogs. The former, however, stated that in all severe cases in rats there were hemorrhages in the central nervous system, and consequent degeneration of the neural elements. Smith, moreover, described marked degeneration in the dorsal column and some in the ventral column of the spinal cord of polyneuritic dogs. Wallerian degeneration of the phrenic, vagus and sciatic nerves in patients with beriberi is often reported at autopsy. Vedder [50] stated the belief that the hoarseness in infants with beriberi is probably due to degeneration of the pneumogastric nerves, with consequent paralysis of the laryngeal nerves. Manson, likewise, believed that one of the symptoms of beriberi in children was subacute meningitis, retraction of the head, drowsiness and rotation of the eyes. Hoobler [51] similarly observed the frequency with which meningismus occurred in infants in the Philippines who had beriberi. Andrew [35] reported extensive involvement of nervous tissue observed at autopsies in infants; he found that the meninges of the brain were congested and edematous, and that frequently the cerebrospinal fluid was increased. Unless the disease has progressed too far, vitamin B therapy promptly results in cures without

47. Nelson, V. E.; Baldwin, F. M.; Riggs, H. G., and Cunningham, M.: The Relation of Vitamin Deficiency to Muscle Fatigue, Am. J. Physiol. **72**:69 (March) 1925.

48. Cowgill, G. R.: A Contribution to the Study of the Relation Between Vitamin B and the Nutrition of the Dog, Am. J. Physiol. **57**:420 (Oct.) 1921.

49. Hofmeister, F.: The Beriberi of Rats, Klin. Wchnschr. **1**:522, 1922.

50. Vedder, E. B.: Beri-Beri, New York, William Wood & Company, 1913.

51. Hoobler, B. R.: An Attempt to Define the Symptomology of Vitamin "B" Deficiency in Infants, Paper Read Before the Fortieth Annual Meeting of the American Pediatric Society, Washington, D. C., 1928.

apparent residual lesions. This probably indicates that extensive involvement of the nerves is not present until after convulsions are well established; such involvement is not apt to occur in the United States where diets are not as devoid of vitamin B as in some oriental countries.

There seems to be some relationship between vitamin B and the hemopoietic system, since the deprivation of this factor brings about certain hemorrhagic conditions in the organism. Moore and Brodie [41] have been able to to produce experimentally a hemorrhagic condition analogous in many respects to that found in infants showing hemorrhagic diathesis. They were able to induce in young rats punctate hemorrhages in the cerebral cortex, mostly in the anterolateral portion of each hemisphere. Hemorrhages also occurred in the genito-urinary, gastrointestinal and respiratory tracts. Sure [52] recently verified Findlay's [53] observations that there is a disturbance in the hemopoietic system consisting of congestion and hemorrhages in the bone marrow of pigeons and rats on a vitamin B-free diet. Funk,[54] furthermore, found in patients who had died of beriberi pinpoint hemorrhages in the stomach, duodenum, kidneys and other organs and occasionally in the sheath or between the fibers of the peripheral nerves. Hofmeister described hemorrhages in the cerebellum and medulla and said that he believed that the condition should be described as cerebral purpura.

The exact physiologic rôle of vitamin B in the body is not known. Various investigators have attempted to show a relationship between this vitamin and the oxidative processes of the body. Drummond,[42] however, demonstrated that the changes in the oxidative mechanism, such as the sharp fall in temperature, in weight, in oxygen consumption and in blood sugar, which occur with convulsions may be produced in control animals merely by withholding food; they are, therefore, due to starvation. Others believed that vitamin B acts as a stimulant or as a catalyst in the body. Funk [54] refuted this idea, and said that he was of the opinion that this substance is a "building-stone" and is actually used up in tissue formation. Plimmer and his associates,[43] extending this idea, advanced the theory that vitamin B is a constituent of every cell, particularly of the nucleus, and that its rôle in the body is to replace the wear and tear of the nucleus and to aid in the growth of nuclear material, more being required for the growing young. This may be an

52. Sure, B.: Dietary Requirements for Fertilization and Lactation: XV. The Inefficiency of the Lactating Mother (Mus Norvegicus Albinus) in Secreting Vitamin B in the Milk, and the Relation of This Phenomenon to Infant Mortality, J. Biol. Chem. **76**:685 (March) 1928.

53. Findlay, G. M.: The Relation of Deprivation of Vitamin B to Body Temperature and Bacterial Infection, J. Path. & Bact. **26**:485, 1923.

54. Funk, C.: The Vitamins, Baltimore, Williams & Wilkins Co., 1922, p. 291.

explanation of the fact that substances rich in nuclear material, such as glandular tissues, yeast and the germ of cereals, grains, etc., are the most potent natural source of vitamin B. This vitamin B nuclear constituent theory, also, gives a reason for the quantitative relationship between body weight and vitamin B requirement. Whatever the rôle of this vitamin may be, it is apparent that its exclusion from the diet of man or animal may result in a syndrome including retardation in growth, loss in weight, anorexia, gastro-intestinal disturbances, muscle atrophy and peripheral neuritis.

COMMENT

As sources of vitamin B, it is evident from our experimental work that breast milk and cow's milk are relatively poor, the latter being somewhat superior. The vitamin B value, as judged by tests on rats, is approximately from one-tenth to one-fifteenth that of the vitamin A content of these kinds of milk. The paucity in vitamin B is even more significant when it is realized that in general the dietary and hygienic conditions under which milk is produced may be far inferior to the standards maintained by the Mother's Milk Bureau of Detroit and the Walker-Gordon Laboratories.

The maternal diet plays an important rôle during pregnancy and lactation. Striking examples of this are seen in countries in which the dietaries are notably limited. Thus, certain Filipino and Chinese women during pregnancy are especially prone to develop beriberi, the strain on the mother being too great when it becomes necessary to provide material for a new being in excess of that necessary for her own metabolic processes. Moore and Brodie [41] have suggested a relationship between vitamin B and excessive hemorrhage at delivery as well as hemorrhages in the new-born. After observing the production of beriberi in puppies nursed by Filipino women whose babies had previously died of this disease, Andrew [35] stated: "It seems probable that there is an intimate relation between beriberi in infants and a mother's diet poor in quality and lacking certain necessary elements which are not included in the diet of the mother." This has been verified repeatedly in experimental laboratories. In the Philippines the dietaries are strikingly deficient in vitamin B, and it is in this country that 50 per cent of deaths of infants are due to infantile beriberi. That in the Philippines it is invariably the breast fed infant who develops beriberi is further proof that human milk may contain less vitamin B than cow's milk. The larger proportion of vitamin B in cow's milk is undoubtedly due to the larger quantities of this essential food factor in the cow's diet as compared with that of the human mother's diet; whereas the cow's ration contains alfalfa, ensilage and whole grains, many of the foods of man are highly refined and are consequently devoid of vitamin B. Sure [52] has

demonstrated that the maternal organism dissipates large amounts of this food factor in the metabolic processes of lactation, thus limiting the amount available in the milk.

In addition to possibilities of the vitamin B content of milk being lowered through the maternal diet, the importance of supplying additional vitamin B early to the diet of the child is indicated by clinical statistics in the Philippines where nine tenths of the deaths from beriberi occur between the ages of 1 and 3 months. This, together with the fact that in three weeks [38] polyneuritis develops in dogs on vitamin-free diets, in four weeks [55] in rats and in six to ten weeks [40] in adult Chinese, indicates that there is no appreciable storage of this substance in the tissues. The body, then, has to rely on food for its daily supply of vitamin B to meet the increased demand for this substance during the period of phenomenal generation of new tissue. Fortunately, this vitamin does not undergo appreciable deterioration on heating, drying and ageing, as is true of vitamin A; nevertheless, there are many possibilities that an insufficient amount may be offered to or utilized by the infant. In certain diseases of infectious or dietary origin that are attended by digestive disturbances and poor appetite, there arises the necessity of insuring a sufficient quantity of vitamin B other than that available in the milk.

An excess of vitamin B is not harmful; it is has been found, moreover, that growth, bodily vigor and appetite are better, and that there is a lessened susceptibility to infectious diseases and digestive disturbances when liberal quantities of vitamin B appear in the diet of the young. Successful lactation and reproduction can be attained only when the maternal diet is generously supplied with this essential food component. Supplements, added to the diet of infants, influence growth and well-being mainly from the standpoint of the vitamin content, for milk is usually adequate in proteins, fats carbohydrates and minerals, with the exception of iron. They insure against those borderline conditions of an insiduous nature which Plimmer and others [43] said they believed to be referable to a chronic state of early vitamin B deficiency.

THE ANTIRACHITIC VALUE OF HUMAN MILK AND OF COW'S MILK

It has long been considered that milk was a doubtful source of the antirachitic substance, because such a large percentage of infants, whether breast fed or artificially fed, have developed clinical rickets. Critical experimental evidence, however, has been advanced only recently.

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55. Macy; Outhouse; Graham and Long (footnote 1, second reference).

The data for human milk are somewhat conflicting. Lesné and Vagliano [56] concluded that the antirachitic factor was lacking. Kennedy and Palmer,[57] on the other hand, were able to cure rats that had rickets by feeding them with human milk fat at a minimum level of 8 per cent. Hess [58] reported that from 25 to 30 cc. of this milk daily was sufficient as a protective food for rats, whereas it was ineffective in a curative type of experiment.

Cow's milk has been shown to contain appreciable quantities of the factor D by all investigators who have attempted to determine its titer by the rat test. The minimum curative dose has ranged from 2 to 25 cc. daily, depending on the conditions under which the milk has been produced and fed.

In studying rickets in rats, it must be borne in mind that this abnormality can be produced only when calcium and phosphorus are present in the relative proportion of 5:1, and that an appreciable increase in phosphorus intake results in a prompt deposition of calcium and phosphorus salts in the epiphyseal-diaphyseal region of the bones. In these investigations careful attention, therefore, has been given to the mineral constituents of the basal ration, so that during the feeding of milk the calcium-phosphorus ratio will be maintained at the requisite level. Such a consideration has not been followed in any of the studies carried out on milk.

Under the foregoing conditions, human milk in quantities as large as 40 cc. daily was ineffective in curing rats with rickets or inducing the deposition of lime salts in their bones. In contrast, 30 cc. of cow's milk daily brought about considerable healing as determined by roentgenograms, microscopic examination of the epiphyseal ends of the tibiae and ash analyses of the femora. The curative properties of 15 cc. of cow's milk daily, however, were so negligible as to be indetectable by these methods.

It has been demonstrated by these experiments that fresh whole human milk does not afford protection against rickets to rats, whereas fresh whole cow's milk contains some of the antirachitic factors. Such results are somewhat contrary to clinical experience, for, as Funk [59] stated in 1922: "The number of cases of rickets increases with the rejection of the natural modes of nutrition and the adoption of artificial

56. Lesné, E., and Vagliano, M.: Lack of Influence of Human Milk on Experimental Rickets, Compt. rend. Soc. de biol. **91**:143 (Feb.) 1924.

57. Kennedy, C., and Palmer, L. S.: The Anti-Rachitic Properties of Breast Milk, Proc. Soc. Exper. Biol. & Med. **23**:230 (Dec.) 1925.

58. Hess, A. F., and Weinstock, M.: A Study of the Antirachitic Factor in Human and in Cow's Milk, Am. J. Dis. Child. **34**:845 (Nov.) 1927.

59. Funk, Casimir: The Vitamins, Baltimore, Williams & Wilkins Co., 1922, p. 312.

feeding of infants." Hess,[58] in a recent publication, gave an excellent critique concerning these paradoxic results. It is, therefore, unnecessary to give a detailed discussion on the influence of certain factors in the production and cure of rickets, such as the vitamin moiety, the acid-base balance, the mineral content of the diet, the environment and the rate of growth.

In evaluating the causes for the development of rickets in so many nonbreast-fed infants of the past, it must be remembered that even today the term "artificial feeding" includes not only those formulas adequately constructed from fresh whole cow's milk, but also every type of proprietary infant food on the market. By means of animal feeding tests, we have demonstrated that cow's milk contains a bone calcifying agent identical to that of cod liver oil; but when the results are interpreted in terms of infant feeding, the actual quantity present is too small to be of value. Thus, if the needs of the infant should be based on the amount of milk required to cure rickets in rats, it would be necessary to feed them approximately 5 ounces of milk per pound of body weight. Conversely, if rats were fed on the basis of the milk requirements of the infant, the rat would be allotted 10 cc. daily, an amount grossly insufficient even as a protective agent. It is, then, evident that inadequate dietaries may be presented to the infant at the period when the vitamin requirement per unit of body weight is greatest.

The antirachitic vitamin is essential for the stabilization of calcium and phosphorus metabolism and for the normal deposition of these minerals in the bony framework. The unusual demand for this substance in infancy is due to the fact that the greatest skeletal development occurs during the first two years of life. The obvious explanations of the nonrachitic child, whether breast fed or bottle fed, is that a sufficient amount of the antirachitic factor has been supplied through the food or through the environment to satisfy the developmental needs.

COMMENT

The early administration of the rickets-preventing factor to the infant is essential, since the environment; i.e. the food and sunshine, of the pregnant mother may bring about a predisposition to early rickets in her child. That the prenatal influence is great is judged by the fact that rickets has been reported as early as the third week of postnatal life. Riesenfeld and others [60] were of the opinion that the amount of phosphorus in the blood of the new-born infant determines whether or not

60. Riesenfeld, E. A.; Handelman, I., and Rose, A. R.: Inorganic Phosphorus in Blood of the New-Born — Its Seasonal Variation and Relation to Rickets, Am. J. Dis. Child. **30**:646 (Nov.) 1925.

rickets will develop. Greenbaum, Selkirk, Otis and Mitchell [61] expressed the belief that if the diet of the mother can be made correct in calories and mineral intake during the last three months of pregnancy, while this will not prevent rickets, it will have a controlling influence on the development of this disease in the young. Various people have attempted to enhance the antirachitic value of the milk by introducing into the maternal dietary substances rich in vitamin D. We have found this method ineffective for the rat. Hess [62] and Gerstenberger and his associates,[63] feeding generous amounts of cod liver oil to lactating women, found that vitamin D properties were not conferred to the milk as judged by tests on rats and by the infant. Weech [64] likewise found that while rickets was not prevented by such dietary precautions, the disease apparently was less severe.

In contrast to the ineffectiveness of the maternal diet during pregnancy and lactation, a controlling part is played by sunlight, either natural or artificial. Thus, Hess [62] found that human milk originally lacking in vitamin D became activated through exposure of the mother to ultraviolet light to such an extent that it was possible to cure rickets in rats. By the same means, Gerstenberger induced healing of the ricketic lesion in infants. The opposite effect, however, appears to hold for the cow, since experimental evidence indicates that the antirachitic value of cow's milk can be enhanced by food but not by ultraviolet light.

The greatest obstacle one meets in attempting to supply vitamin D is that so few of our natural foods contain it in amounts sufficient to prevent or cure rickets. It has been definitely demonstrated that milks are of questionable value. Although egg yolk has been used successfully,[65] Hess stated that it cannot be depended on and is much less efficient than cod liver oil. Sunshine and cod liver oil, then, are left as the only two reliable means of supplying this essential factor. Gerstenberger and his associates [66] expressed the belief that either of these may

61. Greenbaum, J. V.; Selkirk, T. K.; Otis, F. A., and Mitchell, A. G.: Effects of Diet During Pregnancy on Development of Rickets in the Offspring, J. A. M. A. **87**:1973 (Dec. 11) 1926.

62. Hess, A.; Weinstock, M., and Sherman, E.: Antirachitic Properties Developed in Human Milk by Irradiating the Mother, J. A. M. A. **88**:24 (Jan. 1) 1927.

63. Gerstenberger, H. J.; Hartman, J. I., and Smith, D. N.: Antirachitic Value of Human Milk, California & West. Med. **27**:40, 1927.

64. Weech, A. A.: The Influence of the Administration of Cod-Liver Oil to the Mother on the Development of Rickets in the Infant, Bull. Johns Hopkins Hosp. **40**:244, 1927.

65. Hess, A. F.: The Therapeutic Value of Egg Yolk in Rickets, J. A. M. A. **81**:15 (July 7) 1923. Casparis, H.; Shipley, P., and Kramer, B.: The Antirachitic Influence of Egg Yolk, J. A. M. A. **81**:818 (Sept. 8) 1923.

66. Gerstenberger, H. J.: Data Concerning the Dose of Antirachitic Factor in the Prevention and Cure of Rickets, Am. J. Dis. Child. **35**:729 (April) 1928.

be given in much smaller quantities than is usually practiced. They have found that one ten minute exposure to ultraviolet light was sufficient to cause 50 per cent healing of the rachitic condition in an infant, and that small quantities of cod liver oil (from 0.4 to 0.75 cc. daily) will prevent rickets, provided prophylaxis is begun early.

CONCLUSION

From our experimental studies, we have shown that average human milk contains approximately the same amount of vitamin A, but only one-half as much vitamin B, as is found in cow's milk. In respect to the antirachitic factor, human milk is deficient, whereas cow's milk contains a small amount. Although it would appear that cow's milk is somewhat richer in some of the vitamins, the possibility is great for the dissipation of these substances through adverse treatment in the preparation of formulas. Thus, the vitamin value of cow's milk formulas may be rendered inadequate for the child through dilution, through use of top or skimmed milk formulas and through oxidation incident to boiling or ageing, whereas none of these factors enter into breast feeding. Certain vitamins, too, apparently are not so completely utilized when presented to the child in the medium of cow's milk. When it becomes necessary to exchange human milk for cow's milk, consideration must be given to the vitamin value of the formula as well as to its protein, fat, carbohydrate and mineral constituents.

In this study, the vitamins have been stressed, because it is in these factors that infant dietaries are so prone to be inadequate. A close correlation has been shown between vitamin underfeeding and a series of ill defined symptoms, such as lowered growth rate, gastro-intestinal disturbances of various types, susceptibility to infections and other factors. Although definite lesions of the advanced disease may not appear, nevertheless, as McCollum [67] says: "The effects on vitality may be very pronounced in cases where a faulty diet is adhered to until clinically observed symptoms are about ready to appear but while no clear cut lesions are detectable."

Although there are many ways in which the young infant may fail to receive or utilize its daily quota of vitamins, many grow and develop without experiencing nutritive disaster when fed either breast milk or cow's milk. This is undoubtedly due, first, to a varied and well balanced dietary and satisfactory environmental conditions of the mother during pregnancy with the result that vitality of the infant is at a maximum; and, secondly, to the fact that milk adequate in quantity and quality has been consumed by the child. The definite influence of prenatal care and

67. McCollum, E. V., and Simmonds, Nina: Newer Knowledge of Nutrition, ed. 3, New York, The Macmillan Company, 1925, p. 282.

diet on the postnatal development of the child shows the necessity of a close cooperation between the obstetrician and pediatrician.

That there is apparently a great factor of safety in vitamins A and B, even of human milk, became evident to us from a detailed study of milk secreted by two healthy American women.[68] Although the milk of one was appreciably lower in vitamin A and that of both was much lower in vitamin B as compared with the pooled variety, their offspring not only grew exceptionally and equally well, but also failed to develop any adverse symptoms attributable to subminimal amounts of vitamins A and B. The development of rickets in both infants by the fourth and fifth months of life was further evidence of the failure of human milk as a protective agent against rickets even when the maternal diet was notably sufficient and well balanced. The adherence of women throughout pregnancy and lactation to dietaries rich in fruit, vegetables, dairy products, glandular tissues, and the like, together with the early presentation of vitamin-carrying foods to the infant, serve as the most potent factors in the production of the nutritionally stabile child.

68. Macy, I. G.; Outhouse, J., and Hunscher, H.: The Variability in Vitamin Content of Human Milks, Am. J. Home Economics, in press.

Pediatric Biographies

SIMON DE VALLEMBERT

JOHN RUHRÄH, M.D.
BALTIMORE

According to Vallembert himself, he was the first to write a book in the French language devoted to the diseases of children, and no one disputes his claim. A sort of anthology in Latin, which Miron, physician to Louis XII made of his writing, is available, but its length discourages the reader unless he is extremely familiar with the Latin of that period. Possibly a number of copies of this rare book exist. I have seen the one in the British Museum, and presumably there is one in the Bibliothèque Nationale, but a morning's search resulted only in disappointment.

Like so many other medical men, Vallembert is known only by his writings, which consist of his book on children, and two other works: "Traité de la conduite des chirurgiens," Paris, 1558, and "Medicamentorum simplicium cognoscendorum methodus Turonibus," 1561.

The book on children, a volume of nearly 400 pages, printed in pleasing type and on good paper, is entitled: "Cinq livres del a manière de nourir et gouverner les enfans des leur naissance." It was printed at Poictiers by Marnefz et Bouchetz, frères, in 1565. The title page discloses the fact that Simon Vallembert was physician to Madame la Duchesse de Savoye et de Berry, "et depuys peu de temps, de monseigneur le Duc d'Orleans." The book itself is inscribed "A la Royne Mère du Roi," Catherine de Medici, with a wish for her perpetual happiness. The book was written chiefly to assist in the care of the little Prince of Piedmont, son of the Duchesse of Savoye, the sister of the queen.

In the preface, the author states that he is familiar with the writings of the physicians of earlier times, comprising books in Greek and Arabian as well as in Latin. He names, however, the work of Miron as the chief source of his material.

The five books are: "How to Choose a Nurse Well"; "Instructions to the Midwife and Nurse in the Care of the New-born Infant"; "The Method of Nourishing and Caring for the Infant after Weaning," and lastly, "The Method of Curing the Diseases of Children."

He gives his information and instruction in great detail. He believed, with Avicenna and Jaques des Pars, that the mother ought to nurse her own child. If a wet-nurse is needed, he suggests one "whose habits are good and praiseworthy, a woman diligent, pleasant, gracious, chaste,

sober, clean, cheerful and laughing for the child, slow to anger, not easily frightened and not to be suddenly depressed or worried."

The second book is extremely interesting with its minute directions, which are fully as voluminous as those of the present day and in the main not unlike them. Many contemporaneous writings convey the idea that infants were not cared for in earlier periods. The work of Vallembert contradicts this belief with chapters on the care of the eyes, ears and mouth, the linen, the cradle, how to bathe the infant, how to dress it and how to put it to sleep in its crib. The title of one chapter is "Of putting something in the mouth of the infant and of making it sleep—of which two, one should do the first."

Several pages are devoted to a discussion of the use of honey, and an entire chapter to oil of sweet almonds. Vallembert is quite modern in his insistence on a daily sponging or bath for the child, advice which could well be reprinted. He mentions in which vessels the infant should be bathed, the temperature of the water and the length of the bathing period; he tells how to take the child from the bath, how to dry it, how to make it urinate, how to rub it and how to brush its hair.

Not long ago a book was written on exercise for the infant. It is interesting that Vallembert devoted considerable space to the same subject.

He explained why women and children weep oftener than men, and described the different cries of the child. He apparently was ignorant of psychoanalysis, a fact which was possibly in his favor.

Vallembert believed that as soon as the child cut its first teeth, it should have solid food, a belief which was shared by Galen. He describes bread soup and *panade*, the latter evidently a tasty dish made of bread crumbs, bouillon, milk and vegetables. Directions for the preparation of *panade*, which might well be copied in modern books, are as follows:

> In place of bread soup the infant may sometimes be given *panade* made in this manner. Grate or crumble or rub bread into small bits, then place it in a bouillon of good meat in a little glazed earthenware pot and cook it over a small fire of coals, which does not smoke, stirring it with a silver or wooden spoon. Sometimes it may be cooked in a bouillon of peas or other vegetables with oil or butter; oftener, it is cooked with goat's or cow's milk or milk of sweet almonds. Sometimes before cooking the bread is soaked in warm water to eliminate the salt and yeast: some add the yolk of an egg or the whole egg, taking care that it is not broken in cooking, especially if the *panade* is made only with water and butter, or with milk, particularly with the milk of almonds. On this food even the children of princes are nourished.

Almost half the book is devoted to the disease of infants and children. It is somewhat long drawn out and is chiefly a repetition of ancient and Arabian teachings. The work of Galen is quoted. Measles

CINQ LIVRES,

De la maniere de nourrir

ET GOUVERNER

LES ENFANS DES LEVR

NAISSANCE

PAR

M. Simon de Vallambert, Medecin de madame la Ducheſſe de Sauoye et de Berry, et depuys peu de temps, de monſeigneur le Duc d'Orleans.

A POICTIERS,

Par les de Marnefz, & Bouchetz, freres.

1565.

Title page of Vallembert's "Cinq Livres."

and smallpox are considered together and blamed on a common cause—vestiges of the menstrual blood of the mother. The remarks on the prognosis of both diseases are extremely interesting. Consider the clinical acumen contained in one sentence: "Those which are green, or violet, or blackish are dangerous and even the more so, if the patient also has pain about the heart; and if the fever persevere and does not remit, there is scarcely any hope."

The views of Vallembert on medication are sound. Physicians of all ages have learned by experience not to do too much. He recommends, as did others whom he copied, that medication be used externally as far as possible so as not to upset the stomach. "The medicines which one gives to children should be benign and not devoid of all nature of food; neither should they be strong in their nature nor in dose and quantity." This sage advice is found among the errors which Vallembert accepted from his medical forbears in this somewhat rare volume.

News and Comment

BOSTON'S NEW MILK REGULATIONS

"SECTION 1. On and after January 1, 1929, all raw milk, offered for sale in the City of Boston, shall be drawn exclusively from tuberculin tested and accredited herds, or tested herds on the way to accreditation; shall be certified by the Medical Milk Commission in the manner required by law; and shall, when offered for sale, contain not more than 10,000 bacteria per cubic centimeter.

"SECTION 2. On and after January 1, 1929, all milk not meeting the requirements as contained within Section 1, before being offered for sale, shall be pasteurized and shall comply with the following requirements: shall be natural cow's milk not more than seventy-two hours old when pasteurized; shall have a bacterial content of not more than 750,000 per cubic centimeter before pasteurization; shall be subject for a period of not less than thirty minutes to a temperature of not less than 140 degrees Fahrenheit; and shall be immediately cooled to a temperature of 50 degrees Fahrenheit or lower."

"SECTION 5. All cream and skimmed milk offered for sale, not obtained from milk meeting the requirements of Section 1, shall be pasteurized in accordance with the provisions of Section 2, or obtained from pasteurized milk.

SECTION 6. All ice cream offered for sale shall be manufactured from cream obtained from milk meeting the requirements of Section 1, or from pasteurized milk, as defined in Section 2."

"SECTION 8. Pasteurized milk when offered for sale shall contain not more than 50,000 bacteria per cubic centimeter" (from *New England J. Med.*, Dec. 6, 1928, p. 1173).

Provisions are made for the handling and marketing of milk; its pasteurization is regulated, and the two particular weaknesses of pasteurization, unheated foam and cold pockets, are specifically banned.

UNIVERSITY NEWS

Additional Gift for Children's Ward of the University Hospital.—Dr. Harold K. Faber, professor of pediatrics, Stanford University School of Medicine, San Francisco, has received an additional gift of $1,000 from Edward M. Mills for free beds in the children's ward of the University Hospital.

Abstracts from Current Literature

Anatomy and Physiology

VARIATIONS IN THE DEVELOPMENT OF THE BACKBONE, DECEIVING FROM A DIAGNOSTIC POINT OF VIEW. R. J. HARRESTEIN, Nederl. Tijdschr. v. Geneesk. **72**:4011, 1928.

A comparative roentgen and anatomic (microscopic) investigation of a series of nineteen parts of the backbone, from persons between the ages of 1 and 22 years, showed that in the development of the vertebral bodies variations occur which may also be visible in the roentgen-ray pictures and may be confused with pathologic conditions.

1. On the lateral view of the vertebral bodies of children, fissures, described by Hahn (1922), are often visible in the middle of the vertebral bodies; these fissures arise from the front and penetrate more or less far to the back. In adults these fissures or cavities are sometimes confined to one vertebra. After trauma they could be interpreted wrongly as a symptom of vertebral fracture.

2. On the lateral views of persons between the ages of 3 and 16 years, the front of the vertebral bodies sometimes shows the curves described by Hanson (1926), which are caused by an excess of cartilage and which do not have any pathologic significance.

3. The deposit of chalk in the growing disks of the vertebral bodies often shows a large variation in regard to the time of appearance and localization. However, a pathologic condition could never be found as the cause of these large variations.

4. The "Knörpelknötchen" described by Schmorl (1927) in the already ossified vertebral bodies may be visible on the roentgen-ray picture (Man, 1928). The author also found them in four cases. One should be careful not to take them for tuberculous areas, especially when they are visible in only one vertebra.

VAN CREVELD, Amsterdam.

Pathology, Bacteriology and Biochemistry

THE LESIONS IN ANIMALS INOCULATED WITH STREPTOCOCCUS CARDIO-ARTHRITIDIS. WILLIAM P. BELK, FRANK J. JODZIS and EDWARD FENDRICK, Arch. Path. **6**:812 (Nov.) 1928.

Streptococcus cardio-arthritidis has been isolated frequently by Small and Kreidler from the blood of patients suffering from acute rheumatic fever. All strains were biologically similar and were considered to constitute a specific serologic group. Eight rabbits and two horses received repeatedly injections of large doses of the organism. Among the lesions found at autopsy were mural and valvular endocarditis, epicarditis, nonpurulent focal myocarditis and arteritis. In one rabbit, interstitial myocardial lesions were found which were indistinguishable from typical Aschoff bodies. In another rabbit, the lesions on the valves resembled the verrucae found in rheumatic fever.

THE HISTOGENESIS OF ESSENTIAL LIPOID HISTIOCYTOSIS (NIEMANN-PICK'S DISEASE). WILLIAM BLOOM, Arch. Path. **6**:827 (Nov.) 1928.

This study is based on an examination of the organs in a series of five cases of Niemann-Pick's disease. Gross examination showed that the spleens were all greatly enlarged, and except for the presence of malpighian bodies, the normal structure was replaced by a yellowish fatty material. In all cases except one, the liver was yellow and enlarged. The size of the lymph nodes varied. The lung tissue showed a pale gray streaking which was most distinct under the pleura.

The other organs did not disclose any gross changes except that the subcutaneous fat in the late stages of the disease was greatly reduced.

Microscopically, however, changes were seen in practically all the cells and tissues of the body, including the blood. These consisted of (1) the presence of numerous phagocytic cells filled with fat droplets, the nucleus of which resembled that of the histiocyte, and (2) a fatty degeneration in the epithelial cells of the glands, and in the different types of muscle, cartilage, ganglion and glia cells. The phagocytic cells, termed "foam cells," may be seen to develop from the resting endothelial and Kupffer cells in the liver, from the reticulum cells of the lymph nodes, the reticulum cells (exclusive of the littoral cells) in the spleen and bone marrow, from the reticulum cells of the medulla of the suprarenal gland, from the septum cells of the lung, from the resting wandering cells of the connective tissue and the perivascular embryonic cells and phagocytes all over the body. The intravascular agranulocytes also develop into lipoid-filled macrophages in the lung and kidney. It is not apparent that fibroblasts or peripheral vascular endothelial cells can develop into lipoid-storing cells. The reactions of the sections of tissue to various methods of staining indicate that the stored lipoids are probably lecithin.

The condition must be considered as one of congenital lipoid dystrophy the mechanism of which is not yet understood. A practical clinical point is the finding of droplets of lipoid in the agranulocytes of the blood.

THE EFFECTS OF AMNIOTIC FLUID ON SEROUS SURFACES. SHIELDS WARREN, Arch. Path. **6**:860 (Nov.) 1928.

To determine the effect of amniotic fluid in preventing peritoneal adhesions, guinea-pigs were used. Serous surfaces of the intestine were rubbed in eight or ten places with dry gauze until they bled, and the lining of the peritoneal cavity was scraped with a small knife. Forty-four pigs were used as controls. In about 100 other animals, some form of amniotic fluid was left in the peritoneal cavity at the time of the operation. Results showed that the amniotic fluid was of decided benefit in preventing adhesions. Amniotic concentrate prepared by Eli Lily and Company was used in eighty cases. Forty-two of these did not show any adhesions; twenty-eight cases showed slight, five cases moderate, and five cases dense adhesions.

LESLIE, Evanston.

PITUITARY AS ACTIVATOR OF THE GONADAL FUNCTION: RESULT OF THE LATEST RESEARCHES OF STEINACH AND KUN. HARRY BENAMIN, M. J. Rec. **128**:27 (Sept. 5) 1928.

The generative gland of the embryo is under the influence of the maternal pituitary gland and the sex characteristics are developed up to an infantile state which is completed at birth. Then, the anterior lobe of the pituitary gland of the infant does not function; the internal secretion of the infantile sex gland is dormant and the sexual characteristics do not mature, because the infantile body is not equal to a sudden sexual precocity. After the organism has been developed and strengthened, the pituitary assumes its activating function. The secretion of the sex gland becomes active, and the glands rapidly grow to maturity. This state lasts up to senescense; then decline sets in. The pituitary grows inactive; the secretions of the generative glands cease; the entire endocrine system suffers through the cessation and the sex glands retrogress, thus causing the disappearance of the state of maturity. The sequence of events shows the importance of the pituitary in the mechanism of development, and establishes a biologic law of puberty.

WILLIAMSON, New Orleans.

HEPATIC EFFICIENCY: THE VALUE OF THE HEMOCLASTIC AND THE LEVULOSE TESTS IN CHILDHOOD. MURIEL J. BROWN, Arch. Dis. Childhood **3**:14 (April) 1928.

An investigation of the hemoclastic crisis and the levulose test in normal and abnormal conditions of childhood was undertaken to determine the value of these

tests as indicating disease of the liver. The leukocytic changes were observed, after the ingestion of milk, in twenty normal children ranging in age from a few weeks to 12 years. The test was also done with ten children suffering from disease of the liver, and fifteen children with probable disease of the liver. The results obtained were so inconsistent that the author feels that the hemoclastic test is of no value in estimating liver efficiency.

The levulose test was done on twenty normal children. The average increase in blood sugar was 15 per cent. The blood sugar had returned to normal within one and one-half hours after the ingestion of levulose.

In twenty-five cases of certain disease of the liver, nineteen showed an abnormal increase in blood sugar and also showed a delay in the return to the normal. The levulose test gave no evidence that the liver is affected in ketosis or celiac disease. The test is of value in determining liver efficiency.

KELLY, Milwaukee.

FAT AND CHOLESTERIN IN THE LUNGS OF CHILDREN UNDER NORMAL AND PATHOLOGICAL CONDITIONS. SYLVIA GANDOLFO, Riv. di clin. pediat. **26**:187, 1928.

An analysis of the fat in normal and pathologic lungs is given in the accompanying table.

Condition of Lung	Fat, Per Cent	Fatty Acid, Per Cent	Cholesterin, Per Cent	Number of Cases
Normal	9.40	5.51	2.79	3
Pneumonia	11.68	3.21	3.66	8
Bronchitis	7.44	5.75	3.01	2
Atelectasis, etc.	8.07	5.97	2.37	4

The author makes the deduction that cholesterol does not play a part in the respiratory function of the lung, but that other fatty bodies presumably do.

HIGGINS, Boston.

THE RESULTS OF THE TREATMENT OF RICKETS WITH MILK, IRRADIATED IN A CARBON DIOXIDE ATMOSPHERE. K. SCHEER, A. FUHRBERG and A. KOSS, Arch. f. Kinderh. **84**:161 (June 15) 1928.

In forty-two cases, the same favorable results were obtained by this method as were recently reported by Scheer and Rosenberg. In the entire year's work, injurious results have not been seen. This method cures persons with rickets as effectively as any other, and it is far cheaper. There is no disagreeable taste or odor imparted to the milk by the irradiation, and the milk may subsequently be pasteurized or boiled. It should have a particular importance in the field of prophylaxis, as from four to eight weeks of treatment seems to be sufficient in moderately severe forms of rickets. Large amounts are not necessary. The usual quantity given in the cases reported was between 300 and 500 cc.

THE USE OF CITRIC ACID WHOLE MILK AS A MEANS OF COMBATING INFANT MORTALITY AND RICKETS. H. WEISSENBERG, Arch. f. Kinderh. **84**:200 (June 15) 1928.

Weissenberg used citric acid whole milk for three years and nine months in the artificial feeding of sick and well infants under the care of the municipality of Gleiwitz. There has been a remarkable decline in the infant mortality during the past seven years. In 1921, it was 10.1 per cent. In 1923, it was 8.3 per cent. In September, 1924, the use of citric acid whole milk was begun; the mortality for that year was 5.9 per cent. For the next two years, it was 3.3 and 3.2 per cent, respectively, and for 1927, 2 per cent; 1,282 infants were cared for, in and outside of institutions, during that year. During the same period of seven years, the mortality for infants of the city who did not receive municipal care varied between 18.2 and 14.3 per cent, and did not show a regular decline. The author believes that

the remarkably low mortality of the infants receiving municipal care in the last three years is due to the use of citric acid whole milk.

BACTERIOLOGIC OBSERVATIONS IN THREE CASES OF INFLUENZAL MENINGITIS. F. W. SCHEMBRA, Arch. f. Kinderh. **84**:302 (July 20) 1928.

Pfeiffer bacilli were found in the spinal fluid in the three cases reported by Rullmann (*Arch. f. Kinderh.* **84**:299 [July] 1928). Organisms were not found in the blood.

SANFORD, Chicago.

PROBLEMS IN ORGANIZING PROPHYLAXIS AGAINST RICKETS. R. BAMBERGER and DEGKWITZ, Gesundheitsfürsorge f. d. Kindesalter **3**:181, 1928.

The authors believe that ergosterol can cause serious damage to the organism in persons with tuberculosis. After giving from 0.2 to 0.4 per kilogram of body weight for from five to six days, they discovered red blood cells, casts and albumin in the urine. Irradiated milks did not cause any damage and should be used in the prophylaxis of rickets until the question of damage from ergosterol has been settled.

PROBLEMS OF PROPHYLAXIS OF RICKETS. H. VOLLMER, Gesundheitsfürsorge f. d. Kindesalter **3**:192, 1928.

The author suggests that the antirachitic substance, whether it is irradiated cholesterol, irradiated yeast or irradiated ergosterol, should be baked with zwieback so that every child would obtain the antirachitic substance during the third month of life. In Germany, of course, zwieback is an essential part of the standard diet for infants.

REICHLE, Cleveland.

CONDITIONS NECESSARY FOR AMINO FORMATION BY B. COLI. GEORGE ROSKE, Jahrb. f. Kinderh. **120**:186 (June) 1928.

Roske gives credit to Ackerman for having first demonstrated histamine formation by bacteria from histidine. Other observers found that the thyphoid-coli group possessed the property of forming amines.

The author isolated twenty-two strains of *B. coli* from the stools of infants suffering from dyspepsia and intoxication. These he studied in various mediums and under various conditions.

He found that *B. coli* does not form amines in peptone bouillon, which on incubation becomes alkaline. However, in grape sugar bouillon there is a pronounced amine formation (tyramine and histamine). Such amino formation depends on the reaction of the nutrient medium and occurs only in an acid medium. Excess of lactic acid, however, inhibits formation of amines.

ARTHUR ABT, Chicago.

ANEMIA CAUSED BY GOAT'S MILK. W. GRAEVINGHOFF and C. NEUHAUS, Monatschr. f. Kinderh. **40**:71, 1928.

In a child with anemia caused by a diet of goat's milk who was dying of pneumonia, the characteristic red cell condition was a preponderant microcytosis with a noticeable hyperchromic megalocytosis and a small number of nucleated red cells with some megaloblasts. The white cell count did not show a change, in spite of the infection. Thrombocytes were diminished to 173,000.

IMMUNOLOGIC STUDIES OF PNEUMOCOCCUS INFECTION. W. POCKELS, Monatschr. f. Kinderh. **40**:238, 1928.

In the sputum of children with bronchopneumonia and the pleural exudates of persons with empyema, type IV pneumococcus is frequently found. In fact, agglutination reactions show that type IV plays a greater part in the disease of children than in that of adults. The serum in children convalescing from lobar pneumonia contains substances which are bactericidal for type I but not for type IV.

The serum of new-born infants does not show a reaction against either type I or type IV. Following bronchopneumonia, pharyngitis, bronchitis and empyema, the serum does not contain substances which are bactericidal for even the isolated strains. Of all the therapeutic serums tested, the agglutination reactions were only apparent against type I pneumococcus. In some experimental work, the results suggested that a certain degree of immunity to type IV pneumococcus could be obtained in mice by feeding them large doses of a culture.

VARIATIONS IN THE INTESTINAL FLORA OF PREMATURE INFANTS FED ON BREAST MILK. A. SENGENHOFF, Monatschr. f. Kinderh. **40**:263, 1928.

The author showed that the bifidus flora of premature infants fed on breast milk is subject to variation. When the child suffers from diarrhea, frequently there is a diminution of *B. bifidus* and an increase in *B. coli*. In severe forms, the stools show almost pure cultures of colon bacilli. The latter cases are fatal. When colon bacilli increase in the stools of infants fed on breast milk there is an associated coli bacteriuria.

GERSTLEY, Chicago.

WIDAL'S HEMOCLASTIC CRISES IN INFANTS. L. O. FINKELSTEIN, R. A. WILFAND and N. A. SPIZYNA, Ztschr. f. Kinderh. **44**:245 (Oct.) 1927.

The method worked out by Widal for the determination of the functional capacity of the liver is not adapted for use in children. The statement of Schiff and Stransky that leukopenia appears to be a physiologic reaction in digestion, is not substantiated by facts.

EMERSON, Boston.

THE DISTRIBUTION OF BISMUTH IN THE BLOOD. SVEND LOMHOLT, Ugesk. f. Laeger **90**:751, 1928.

The analyses made indicate that almost the entire amount of bismuth in the blood stream is combined with the various fractions of the plasma proteins. A small amount of bismuth is found in the leukocytes. The erythrocytes, lipins and ultrafiltrate of the plasma contain scarcely any demonstrable amounts of bismuth.

SCHLUTZ, Minneapolis.

QUANTITATIVE ESTIMATION OF DIASTASE IN RACHITIC URINE IN JAPAN. O. OMORI and S. YAMANE, J. Pediat. (Tokyo), April, 1928, no. 335, p. 717.

The authors endeavored to determine the quantity of urinary diastase in the rachitic children in Japan by means of a quantitative method, as devised by Adam in 1923. On the whole, they found that the quantity of diastase is increased, often to a remarkable degree, in the urine of rachitic children. Sometimes the quantity is not absolutely increased. In young infants, the quantity of diastase is small, and even in rachitic infants, there is no noticeable difference as compared with that of normal infants. In cases in which the quantity of diastase is increased, the diagnosis of rickets may be made long before the bony changes are evident.

KATO, Los Angeles.

THE INFLUENCE OF DYSENTERY TOXIN ON SURVIVING MUSCLE TISSUE FROM THE STOMACH AND INTESTINE OF THE RABBIT. K. SUZAKI, Orient. J. Dis. Inf. **2**:139, 1927.

The effect of dysentery toxin on surviving smooth muscle tissues from the stomach and intestine of the rabbit was studied. Five types of dysentery bacilli were used which gave similar results. The toxins caused an increase in the frequency and intensity of the movements of the muscle from the stomach, duodenum and jejunum and a decrease in those of the muscle from the ileum, colon and rectum. The active principle of this reaction is found in the alcohol soluble portion of the dysentery bacilli and not in the ether soluble lipoid.

HIGGINS, Boston.

Nutrition

BREAST FEEDING. JESSE R. GERSTLEY, M. Clin. N. Amer. **12**:185 (July) 1928.

Gerstley was enabled to make some interesting observations on the food intake of two breast-fed infants through the cooperation of the mother, who weighed them before and after nursing for a period of several months. The most surprising fact noted was the great variation in the amount taken during the feedings. One infant at the age of 4 weeks, took as much as 9½ ounces (281 cc.) of milk during one feeding, and as little as 4 ounces (118.4 cc.) during another feeding on the same day. The total amount taken varied from day to day, but not to such a degree as did the individual feedings. This infant nursed vigorously and gained rapidly. His brother was less voracious, took less milk and exhibited less variation in individual nursings and the total daily amount consumed. He gained more slowly and bottle feeding became necessary at an earlier period.

The author summarizes some of his work, recently published, on the chemistry of breast milk and the acids of the infant stool. Attention is called to the fact that regardless of the physical character of the stool of a breast-fed infant, its twenty-four hour weight and acidity remain practically uniform. This condition is maintained in spite of the addition of double or treble the normal amount of lactose, thus demonstrating the marvelous mechanism existing in the reaction between breast milk and the intestinal tract of the child.

SMITH, Ogden, Utah.

FUNCTIONAL VOMITING IN NEW-BORN AND PREMATURE INFANTS. W. M. EMBDIN, Arch. Dis. Childhood **3**:262 (Oct.) 1928.

To study vomiting in the new-born infant, an investigation was made of 300 consecutive cases during the first week of life. Only 64, or 21.3 per cent, of the infants presented true cases of vomiting. The condition existed irrespective of the sex of the infant. There was more vomiting in the premature and weak infants. Vomiting usually began at about the end of the first day or during the second day of life, when milk was first assimilated. It increased in frequency during the second and third days. Then it continually decreased in frequency and amount. By the sixth or seventh day few infants vomited. Usually there was little force exerted. In the sixty premature and weak infants studied it was found that the smaller the weight at birth the greater the tendency toward vomiting, infection and death. The vomiting starts slowly, but soon grows more frequent, obstinate and copious in the premature infants. In this group especially, the presence of bile is important.

Vomiting in the infant differs from that in the adult. The pressure of the abdominal muscles plays a small part and the act is far less unpleasant and more easily initiated. Roentgen and clinical investigation show a tendency toward relaxation of the cardiac sphincter. The sympathetic system is insufficiently developed. The nervous action in new-born infants is chiefly vagal, resulting in vagotonia. A tendency exists, therefore, toward increased movements of the intestine and toward vomiting.

PETERMAN, Milwaukee.

RECENT CLINICAL CONCLUSIONS REGARDING THE DIGESTION AND UTILIZATION OF THE STARCHES IN THE FIRST MONTHS OF LIFE. G. C. BENTIVOGLIO, Riv. di clin. pediat. **26**:96, 1928.

Children are able to digest starch even in the first week of life. They are able completely to utilize 1 Gm. of flour per feeding every three hours during the first month, from 2 to 3 Gm. the second month, and from 4 to 6 Gm. after the third month. Breast-fed infants utilize starch better than artificially fed infants. The author draws his conclusions from clinical observation, examination of the stools and blood sugar curves.

OLIVE OIL IN THE FEEDING OF INFANTS. D. MOGGI, Riv. di clin. pediat. **26**:204, 1928.

The author reviews the results obtained in the pediatric clinic in Florence with a mixture containing varying proportions of cow's milk, water and sugar, flour (usually rice flour) and olive oil. Seventeen cases among infants of different ages and in which feeding was difficult are reviewed.

The conclusions drawn are:

1. The mixture is well tolerated by infants, even better tolerated when olive oil is not included.

2. Infants fed with this mixture seem to overcome intestinal and parenteral infections readily. In tuberculosis, it gives good results.

3. Children with intolerance for fat seem to tolerate olive oil well. It does not appear to be laxative.

The amount of olive oil used was from 1 to 3 per cent of the volume of the feeding.

IMPORTANCE OF VITAMIN B ON TOLERANCE TO FAT AT A PERIOD OF RAPID GROWTH. G. CAREDDU, Riv. di clin. pediat. **26**:329, 1928.

White rats were put on a diet containing starch, casein, lactose and salts, to which was added, in different groups, (*a*) cod liver oil (rich in fat-soluble vitamin), (*b*) butter (a moderate amount of fat-soluble vitamin) and (*c*) soy bean oil (not fat-soluble vitamin). None of the foregoing diets contained vitamin B.

The effects of these diets were (1) anorexia, (2) loss of weight and extreme malnutrition, (3) low temperature and (4) skin lesions. These symptoms disappeared in a few days when vitamin B was added to the diet. The condition found was independent of the presence of the fat-soluble vitamin.

THE AMINO-ACIDS OF WOMAN'S MILK. C. GIAUME, Riv. di clin. pediat. **26**:356, 1928.

The content of the amino-acids in human colostrum and milk was determined by Folin's reagent (naphthoquinonsulphonic acid) on a filtrate obtained by Benedict-Murlin's method.

The results obtained are given in tables 1 and 2.

TABLE 1.—*Results of Tests for Amino-Acids in Human Colostrum and Milk*

Number of Cases	Day of Puerperium	Colostrum Amino-acids, Mg. per 100 Cc.	Day of Lactation	Milk Amino-acids, Mg. per 100 Cc.	Difference, Mg. per 100 Cc.
3	2d	11.45	7th– 8th	7.10	4.35
4	3d	8.67	9th–12th	5.40	3.27
Average.....		9.86		6.10	3.74

The same mothers were used in this comparison.

TABLE 2.—*Results of Tests for Amino-Acids in Human Milk*

Number of Cases	Month of Lactation	Amino-acid Content of Milk, Mg. per 100 Cc.
10	1st to 3d	5.70
9	4th to 6th	4.90
7	7th to 9th	6.68
6	10th to 13th	5.19
6	13th to 18th	5.25

The figures show that the amino-acid content of the milk is one-fourth less than that of the blood. The amino-acids of the blood doubtless serve as material for formation of the protein of the milk. The diminished amino-acid content of

the milk as compared with that of the colostrum can be explained by the relative maturity and functional capacity of the mammary gland.

HIGGINS, Boston.

DETERMINATION OF GASTRIC ACIDITY IN INFANTS FOLLOWING A TEST MEAL OF BARLEY WATER. S. MÜLLER and H. GUTSCHMIDT, Arch. f. Kinderh. **84**:250 (July 20) 1928.

A feeding of 125 cc. of barley water was given to infants. To assure a complete emptying of the stomach, six to seven hours were allowed between the previous meal and the feeding. The fluid was withdrawn thirty-five minutes later. In the first year of life, the value of free hydrochloric acid was lower than in older children. For this period, the values were: free hydrochloric acid, 9; combined hydrochloric acid, 14.5, and total acid, 20.5. Children suffering from parenteral disease, without fever and without digestive disturbance, gave a normal reaction; if fever and dsypepsia were present, the acid values were decreased. Cases of scurvy, gout and mild anemia also showed low values.

VITAMINS C AND D IN BANANAS. U. GRÜNINGER, Arch. f. Kinderh. **84**:284 (July 20) 1928.

Experiments were made on animals to determine whether or not bananas purchased in the German market contained vitamins C and D. The presence of vitamin C was proved by the fact that scurvy was prevented in guinea-pigs fed with bananas and that the fruit sufficed to cure scurvy in those which already had the disease. The vitamin D content was established likewise by the fact that rats which were fed bananas in addition to the rachitic diet developed a much lighter form of rickets than that appearing in the animals of the control group. It was not found possible to maintain normal growth in either the guinea-pigs or the rats, but the essential factors which were lacking in the banana diets were not determined.

SANFORD, Chicago.

ACID-BASE RELATIONS IN INTOXICATION. MATILDE OSANN and S. ROSENBAUM, Monatschr. f. Kinderh. **40**:344, 1928.

In a study of alimentary intoxication the author made determinations of the p_H of the arterial blood of dogs under varying conditions. He also determined the carbon dioxide concentration and the alkali reserve. Conditions during the experiments varied from the normal state to periods of exsiccation, endotoxin poisoning and exsiccation combined with endotoxin poisoning. The results of this highly interesting work showed a slight increase toward the acid in exsiccation. A greater shift toward the acid occurs in endotoxin poisoning. By far the greatest acid change occurs, however, when a condition is produced which largely resembles alimentary intoxication and is caused by a combination of exsiccation and endotoxin poisoning.

THE INFLUENCE OF RAW AND STERILIZED BREAST MILK ON THE GROWTH OF PREMATURE CHILDREN. W. CATEL and M. WALLTUCH, Monatschr. f. Kinderh. **40**:354, 1928.

In a study of premature infants nourished with raw and sterilized breast milk, the authors found that the children thrived on from 80 to 120 calories of the raw milk, while from 135 to 150 calories of the cooked milk was necessary for the same gain. Conversely, if the infants fed with boiled milk were given an equal energy quotient, they gained 14.6 Gm. daily, whereas, the group fed with raw milk gained 25 Gm.

The mortality from bronchitis and bronchopneumonia was much higher among the infants fed on boiled milk than among the group receiving raw milk.

GERSTLEY, Chicago.

THE ARTIFICIAL FEEDING OF INFANTS: II. CLINICAL STUDIES OF DRIED MILK. T. SUZUKI, Orient. J. Dis. Inf. **2**:1, 1927.

Eleven case reports are presented in which Japanese children were fed, at different times, (*a*) malted milk and (*b*) dried milk. The children in each case did better on the second group of feedings as to both clinical results and weight. The author does not explain the reason for this fact.

THE ARTIFICIAL FEEDING OF INFANTS: V. FURTHER INVESTIGATIONS, ESPECIALLY OF CASEIN AND VITAMIN C. T. SUZUKI, Orient. J. Dis. Inf. **3**:37, 1928.

Experiments with rats show that the addition of protein (casein) is necessary for proper growth when a diet of malted milk is used.

AN ANALYSIS OF THE IRON CONTENT OF THE ORGANS OF PIGEONS SUFFERING FROM AVITAMINOSIS. K. SAWANISHI, Orient. J. Dis. Inf. **3**:44, 1928.

In pigeons with beriberi produced by a diet of polished rice, there is an increase in the iron content of the liver and bone, and no change in the iron content of the kidney, lungs, brain and pancreas; the amount of hemoglobin in the blood is diminished.

ARTIFICIAL FEEDING OF INFANTS: I. NUTRITIVE VALUE OF DRIED MILK AS FOOD FOR INFANTS. T. SUZUKI, Orient. J. Dis. Inf. **2**:125, 1927.

In Japan, breast-feeding is more prevalent than artificial feeding. Beriberi, rickets and serous meningitis resulting from lead poisoning are frequently found in breast-fed children and are the cause of the high infant mortality in Japan. When children have been weaned for fear of the foregoing diseases, ignorance of the mothers concerning proper methods of feeding has caused even more deaths of infants.

Comparative experiments on prepared dextrimaltose foods (malted milk) and on dried milk preparations (dry whole milk, Klim, Lactogen) were made with rats. Results are based on the growth and behavior of seventeen rats. The rats invariably did better on the feedings of dried milk than of the malted milk.

HIGGINS, Boston.

Prenatal Conditions

THE METHOD OF CARING FOR PREMATURE AND UNDERWEIGHT BABIES AT THE LYING-IN HOSPITAL, NEW YORK CITY. LILA J. NAPIER, Bull. Lying-In Hosp., New York **13**:132 (July) 1927.

A plan is followed in which all premature infants are placed in one room under the care of certain nurses. By means of an ordinary radiator, the heat of this room is maintained at a temperature of between 76 and 80 F. Sufficient moisture in the air is provided by placing water constantly on the hot radiator and by the formation of steam in the small sterilizer. To maintain constant heat in each crib, hot water bottles are placed between the inner and outer sections; the thermometers which are kept in the inner crib register from 80 to 85 F. The infants are removed from their cribs only for special treatments such as injections of saline solution and treatments with the ultraviolet ray; the latter are usually given after the infant is 2 weeks old. Breast milk is used almost entirely for feeding. The Breck feeder or nursing bottle is employed for feeding; whein this is not possible, gavage is used. The amount of milk given at each feeding depends entirely on the infants: 1 or 3 drachms (4 or 8 cc.) is given at first, and this amount is increased as the children are able to retain it. Eight feedings are given during the twenty-four hours.

SOME CONGENITAL ANOMALIES OF THE GASTRO-INTESTINAL TRACT. J. R. LOSEE, Bull. Lying-In Hosp., New York **13**:148 (July) 1927.

An infant with apparent pyloric stenosis did well until the fifth day of life when it began to regurgitate its food. Feedings would be retained for as long as twenty-four hours; then, practically all the nourishment received during that time would be regurgitated at once. This symptom gradually became pronounced and continued until death from inanition occurred on the twenty-fifth day. Stools which were yellow and green in color were passed daily, but they were unusually small in amount. At autopsy, the colon and rectum were collapsed and practically empty. Before death, visible peristalsis was not observed, and the abdominal distention partially disappeared after regurgitation. At postmortem examination, the musculature at the pylorus was not found to be hypertrophied. Neither was there an occlusion of the duodenum or of any portion of the intestinal tract. The condition was apparently caused by a spasm.

Congenital atresia of the small intestine is more frequently observed than is stenosis. The duodenum is the usual site for this anomaly. It has been observed twice in 3,000 autopsies performed during a period of fifteen years; during this time, approximately 70,000 new-born infants were under observation. In an atresia of the duodenum, if the obstruction occurs below the papilla of Vater, there is a frequent overflow of bile into the stomach and on examination the stools do not show pigment.

The more common form of Meckel's diverticulum is situated in the abdominal cavity where it terminates either as a ligamentous process or as a cord floating free, more rarely as a hernial sac and still more rarely in the mesentery. The adherent diverticulum is generally attached to the navel by means of a blind end or as a cord. The open diverticulum discharges at the navel and occasionally extends for a distance from it. The diverticulum is sometimes adherent to a loop of the intestine which has prolapsed as an umbilical hernia; then, too, a portion of the abdominal wall may be absent. It is the latter type which is of interest in the new-born.

SANFORD, Chicago.

Diseases of the New-Born

REPORT OF A CASE OF GANGRENE OF THE CECUM IN A NEW-BORN INFANT. LUCIUS A. WING, Bull. Lying-In Hosp., New York **13**:153 (July) 1927.

The cardinal symptoms of intestinal occlusion in the new-born infant are: vomiting, abdominal distention and failure of the bowels to move in a normal manner. It may be emphasized that although irrigation of the colon may bring away material which appears to be stained with meconium complete obstruction is not ruled out. The prognosis in intestinal occlusion in the new-born infant is rather poor; recoveries, however, have been reported. Surgical treatment must be given early to be of any value. The invasion of the intestinal canal and the subsequent infection of the peritoneal cavity are rapid in these cases.

FETAL AND NEONATAL MORTALITY. MEYER ROSENSOHN, Bull. Lying-In Hosp., New York **13**:167 (July) 1927.

During 1926, the hospital has had in both indoor and outdoor service a total of 4,944 deliveries with 5,000 infants, 216 stillbirths and 136 neonatal deaths. Among these 352 stillbirths and neonatal deaths 182 or 3.6 per cent of the infants were delivered at full term.

SANFORD, Chicago.

CONGENITAL ANEMIA WITH JAUNDICE. HAZEL CHODAK GREGORY, Proc. Roy. Soc. Med. **21**:1730, 1928.

The author reports in great detail a case of jaundice accompanied by anemia in a child aged 24 days. The jaundice was first noticed when the child was 10 hours old. Epistaxis had occurred once, but at the time of the report the child was improving.

WILLIAMSON, New Orleans.

A Case of Curable Induration of the Skin of the New-Born (So-Called Scleroderma of the New-Born). U. de Gironcoli, Riv. di clin. pediat. **26**:165, 1928.

A boy, born at term after a hard labor, was cyanotic; three quarters of an hour of artificial respiration was necessary to make the child breathe satisfactorily. At 10 days of age, indurated areas began to appear on the skin of various parts of the body, especially the neck, upper arm and thigh. The indurated areas were dull, reddish violet, cold, seemingly tender on palpation and about 1 cm. in diameter. The lesions gradually disappeared, and the child did well nutritionally.

The author suggests that the lesions may be due to trauma of the sympathetic nervous system resulting from the asphyxial condition at birth.

Higgins, Boston.

New Conceptions About the Treatment of Asphyxia Neonatorum. H. van der Hoeven, Nederl. Tijdschr. v. Geneesk. **72**:3678, 1928.

The causes of asphyxia in a new-born infant may be different. The irritability of the respiratory center may be lost; the thorax may be too weak; aspiration of amniotic fluid or meconium may have taken place and, finally, a cerebral hemorrhage may have occurred. The author discusses the symptoms and the clinical picture of the different kinds of asphyxia. In regard to the treatment for asphyxia neonatorum, the author emphasizes that one must always think of the possibility that the asphyxia has several causes at the same time. The treatment consists first of cleaning the mouth and throat as well as possible, before the umbilical cord is cut. All further measures must consist in trying to make the child breathe. In most cases this will happen when the child is turned upside down for some time, e. g., half a minute, and is softly tapped on the chest. If these measures are not successful, warm baths, eventually alternated by short cold ones, are given. These measures are preferred to that of striking the nates. When aspiration of the meconium can be excluded, the method of insufflation of air from mouth to mouth may be used as a further measure. Of course, the necessary precautions to prevent cooling should be taken, and at the same time the heart sounds must be controlled now and then. If necessary, cardiac stimulants are injected. The author has never seen certain success from injections of lobeline. If all the measures mentioned do not produce respiratory movements, the methods of Ogata or Schultze may be used, but with little hope of success; for in cases in which all endeavors are in vain, one is nearly always dealing with cerebral hemorrhages, and in these cases especially, the methods of Ogata or Schultze should be rejected.

If the new-born infant once breathes, one should do nothing but keep a strict watch over him. Every attempt to make the infant cry must be strongly dissuaded. If the asphyxia was caused only by a too small irritability of the respiratory center, the child, as soon as it takes a breath, will begin to cry spontaneously after a short time. Also, in cases of a too weak thorax, further stimulations are superfluous. In cases of aspiration of meconium and in those of cerebral hemorrhage extra stimulations will do harm. In these cases it is a mistake to attempt to make the child cry. In the latter cases if the child begins to breathe one has to wait quietly for several hours and then, especially in cases of aspiration of meconium, the conditions will have ameliorated. In cases of cerebral hemorrhage, the prognosis is worse.

Gangrene of the Skin of the Right Foot in a New-Born Infant. K. de Snoo, Nederl. Tijdschr. v. Geneesk. **72**:3915, 1928.

The author describes a rare case of extensive gangrene of the right foot in a new-born infant. The disease appeared directly after birth, probably in consequence of disturbances in circulation. The possibility that the gangrene was caused by strangulation of the foot could be excluded, especially as there were also some gangrenous spots in other places. For this reason the presence of an embolus could also be rejected as the cause, and the existence of contraction of the vessels had to be accepted. The author took the loss of the whole foot for granted and waited for spontaneous demarcation under dry aseptic treatment. After several

days, however, the temperature and color of the foot grew better, and after the separation of the greater part of the skin of the foot a normal foot appeared. The gangrene had probably been restricted to the superficial layers of the skin and had been caused by extensive contraction of the vessels of the skin.

GANGRENE OF THE SKIN IN A NEW-BORN INFANT. J. PRINS, Nederl. Tijdschr. v. Geneesk. **72**:4215, 1928.

After the case described by de Snoo (*Nederl. Tijdschr. v. Geneesk.* **72**:3915, 1928), the author reports a case of gangrene in which the infant was normal at birth. When the child was 3 or 4 days old, however, white spots were noted on the left foot which became blue-violet. The rectal temperature rose to 39.7 C. (103.4 F.), on the thirteenth day. The umbilicus was normal. The left leg became totally gangrenous up to several centimeters above the knee. There was a distinct demarcation, and a total mummification manifested itself. The right leg was normal. The Wassermann reaction was negative. On the fifteenth day the child died; further investigations of the etiology of this rare condition were not made.

NEUROBLASTOMA OF THE SUPRARENAL GLAND WITH METASTASES TO THE LIVER IN A CHILD AGED 18 DAYS. S. M. C. VAN VEEN, Nederl. Tijdschr. v. Geneesk. **72**:4393, 1928.

The author describes a case of neuroblastoma of the Pepper type in the suprarenal gland. When taken to the infants' hospital, a girl, aged 18 days, had a large liver. The clinical diagnosis of malignant tumor of the liver was made. Four weeks later the pathologic and anatomic investigation showed that neuroblastoma sympatheticum with metastases in the liver was present.

The child was born at term, and weighed about 4,000 Gm. The parents, as well as the other children, were healthy. At birth the child's abdomen was enlarged, but after the twelfth day of life the mother noticed a regular increase of the abdominal circumference. In the infants' hospital the child did not have icterus, and the blood did not show any reactions of bile pigments. The spleen was not palpable under the tumor of the liver. The lymph glands were not palpable. Examination of the blood showed that there was a small decrease in the number of erythrocytes and a large leukocytosis with a small deviation to the left.

During the last week of life, a remittent fever was noticed, the highest temperature being 38.3 C. (100.9 F.). Increased vomiting and frequent stools appeared. Finally, a large amount of fat was found in the stool. The size of the tumor in the liver increased steadily. A short time before death, the circumference of the abdomen was 48.2 cm.

At autopsy the primary tumor was found at the back of the abdominal organs, issuing from the right suprarenal gland. The left kidney and the left suprarenal gland were normal. On microscopic examination the suprarenal glands and the tumor of the liver gave the typical picture of neouroblastoma sympatheticum. Insulae of small cells with large dark nuclei and little protoplasm were present. Between these cells were broad bands of vascular connective tissue, in which large blood extravasations were present. A large part of the normal tissue of the liver was replaced by this tumor tissue.

Further investigation showed a metastases only in the right kidney; none was found in the lymph glands. In conclusion, the author discusses briefly the differences between the several types of primary tumors of the suprarenal medulla, especially between the Hutchison and the Pepper types.

VAN CREVELD, Amsterdam.

Acute Infections

ACTIVE IMMUNIZATION AGAINST DIPHTHERIA AND SCARLATINA. W. T. BENSON, Edinburgh M. J. **35**:617 (Nov.) 1928.

This communication deals with the results from attempted active immunization of the nurses in the City Hospital of Edinburgh, during the past six years for

diphtheria and three years for scarlet fever. Commercial preparations have finally supplanted the locally prepared ones for the Schick and Dick tests, 0.2 cc. of toxin solution in each being used. Approximately 58 per cent of the nurses showed positive reactions to the Schick test, and 33 per cent reacted positively to the Dick test. Both toxin-antitoxin and, recently, toxoid preparations have been used for immunization against diphtheria, the latter causing only occasionally local pain and edema, and rarely (in 2 of 221 nurses) systemic reaction. Diphtheria prophylaxis resulted in 95 per cent negative Schick tests within one year, while 7 of 143 nurses showed a diminished susceptibility in from twelve to thirty-one months after injection.

The scarlet fever tests showed that one third of the group of seventy-eight nurses complained of constitutional reaction, either after the first or the second injection of from 1,000 to 5,000 skin test doses. The final dose of from 20,000 to 30,000 skin test doses did not cause any discomfort. As a rule, constitutional symptoms occurred in those persons who showed a large, brilliant, scarlet-red reaction to the Dick test, and with such reactors the course of injection is now modified by giving smaller initial doses of 500 and 1,000 skin test doses, followed by doses of 5,000 and 20,000. A high percentage of positive reactions to the Dick test change to negative within from 2 to 4 weeks after the completion of injections. Tonsillitis is less common than it was formerly before measures for immunization were used.

The result of immunization is shown in the great reduction in the incidence of these two diseases among the nursing personnel. Scarlet fever has been almost abolished among the nurses. The author advises immunization against diphtheria from three to six months before the nurse goes on duty in the contagious wards. The Dick test is, with rare exceptions, a reliable index of immunity, and the active immunization among nurses gives results which bid fair to rival the happy results which follow the application of toxoid-antitoxin injection against diphtheria.

NEFF, Kansas City.

THE VALUE OF SEROTHERAPY IN SCARLET FEVER. P. NOBECOURT, R. MARTIN, P. R. BIZE and A. LAFFAILLE, Presse méd. **36**:1201 (Sept. 22) 1928.

From their studies carried on for one year, the authors conclude that:

1. Scarlet fever antiserum is ineffective in the treatment of the suppurative complications and the secondary infections and septicemic syndrome of scarlet fever; it produces, however, considerable amelioration in the toxic condition if administered early. In infectious, eruptive diseases it is difficult to assert that a drug is truly active; nature and spontaneous cure must always be considered; even when the patient seems lost, the situation sometimes changes spontaneously and cure follows. It is particularly difficult in scarlet fever to affirm at the beginning that a case is of the malignant type. The fact that the patient gets well, therefore, does not prove the efficacy of a serum. It is permissible, nevertheless, to say that the action of the scarlet fever antiserum appears favorable in certain cases.

2. By producing passive immunity the serum can be of definite value in selected cases. This immunity, however, does not last for more than three or four weeks. On the whole, therefore, preventive serotherapy is an inadequate method of prophylaxis.

THE CLINICAL COURSE AND THERAPY OF TOXIC DIPHTHERIA. E. KOENIGSBERGER, Arch. f. Kinderh. **84**:265 (July 20) 1928.

After periods of a mild form of diphtheria, the toxic form is most likely to develop. One hundred cases which were studied showed the high rate of mortality of 80 per cent. They may be divided into four groups: the first, the simple tonsillar and nasal form of diphtheria; the second, diphtheria with laryngeal complications; the third, with infection of the kidney and heart, and the fourth, the hemorrhagic form of diphtheria. In the first two groups the mortality was

only 7 per cent, but the percentage of complications was high, 27 per cent of the patients having circulatory disturbances, 7 per cent, nervous disturbances and 17 per cent, both. Koenigsberger gives large doses, about 50,000 units of antitoxin. He also supports the system by the administration of strychnine and finds that atropine decreases the respiratory congestion.

IMMUNIZATION AGAINST CHICKENPOX. K. VON KÉSMÁRSZKY, Arch. f. Kinderh. **85**:1 (Aug. 31) 1928.

In fifty of a series of fifty-one cases, the author was able to produce immunity against chickenpox by intracutaneous injection of 0.1 cc. of citrated blood from a patient with chickenpox. This blood was always withdrawn within thirty-six hours of the appearance of the disease. There was no local or general reaction, or any undesirable results manifested. The length of the period of immunity was not determined.

SANFORD, Chicago.

HYDROPHOBIA INOCULATED BY FIXED VIRUS OR INOCULATED BY STREET VIRUS AND MITIGATED BY VACCINATION. L. SYLLABA, Čas. lék. česk. **65**:7 (Jan.) 1926.

In 1913, Simon collected reports of a series of 211,779 cases in which inoculation was done, in eighty-four of which secondary nervous manifestations developed. The pathogenesis of these symptoms may be attributed to: (1) rabies of street or "wild" virus, mitigated by inoculation, the fausse rage of Pasteur; (2) rabies due to fixed virus of inoculation (laboratory or rabbit rabies); (3) toxemia due to toxins other than fixed virus; (4) nerve irritation due to anaphylactic reaction of foreign proteins as lipoids or lecithins, or (5) predisposition to neurotrophic infections as a result of the inoculation, mainly acute anterior poliomyelitis, epidemic encephalitis or influenza. The patient in the case cited developed symptoms of acute ascending paralysis after the seventh injection.

STULIK, Chicago.

THE WHITE BLOOD CELLS IN SCARLET FEVER. A. F. PETROFF, Pediatriya **12**:241, 1928.

The author used Schilling's classification of the white blood cells. The white cells were divided into leukocytes, monocytes and lymphocytes. The leukocytes were subdivided into: myelocytes, juvenile leukocytes, single segmented leukocytes and polymorphonuclear leukocytes. Normally, the blood does not contain myelocytes or juvenile leukocytes, and has only about 4 per cent of single segmented leukocytes. In pathologic conditions, there is an increase in the single segmented leukocytes and, at times, juvenile leukocytes or even myelocytes appear; according to Schilling's terminology, a "change to the left" takes place.

The author stained all smears by the Pappenheim method, a combination of May-Grünwald's and Giemsa's stains. At least 200 cells were counted each time. Forty-four cases of scarlet fever were studied, specimens of blood being taken for about six or seven weeks.

The author's conclusions are:

1. The acute stage of scarlet fever is characterized by a neutrophilic leukocytosis and a marked "change to the left."

2. The majority of mild forms of scarlet fever showed an eosinophilia. The severe forms showed either an eosinopenia or a total absence of eosinophils.

3. The eosinophilia usually begins during the second or third day of the disease and reaches its maximum between the third and seventh day of the disease. A secondary rise in the number of eosinophils may be noticed during the fourth and fifth weeks of the disease.

4. The blood in scarlet fever is of diagnostic significance only in cases in which eosinophilia is present; the other changes in the blood occur in many other diseases.

5. The severity of the disease is shown by the type of the "change to the left" (an increase in juvenile leukocytes and myelocytes), and by the degenerative reactions (vacuolization and basophilic degeneration).

6. Uncomplicated forms showed a normal blood picture by the end of the second week.

7. Complications in the serum showed a pronounced "change to the left," mild complications showed only an increase in the polymorphonuclear neutrophils.

8. Schilling's method is of great value in cases of scarlet fever.

GASUL, Chicago.

PROPHYLACTIC INOCULATION OF COCTOPRECIPITIN AGAINST SCARLET FEVER. H. SAITO, Japan J. Infect. Dis. **2**:933 (June 20) 1928.

Because of the frequent severity of reactions from small prophylactic injections of original scarlet fever toxin, as first brought out by the Dicks, the author prepared a toxic filtrate from hemolytic streptococcus by the following method: After growing it in bouillon containing 0.1 per cent goat serum for four days, he passed it through a Berkefeld filter V, and heated it in a water bath which was kept at 100 C. for thirty minutes; the precipitated protein was then removed by cooling the filtrate in an icebox for twenty-four hours. He found that the coctoprecipitin prepared in this way could be given in much larger doses than could the original toxic filtrate. He succeeded in many cases in obtaining a negative reaction to the Dick test by an average of 7,195 skin test doses. He further found that with younger children immunity was established with difficulty, while older children (over 10 years of age) could be immunized rather easily. The author recommends the use of his agent in active immunization against scarlet fever, for it can be given in larger doses and at shorter intervals than can the original toxin, thus adding greatly to the convenience of both the physician and the child.

RECTAL INJECTION OF ETHER FOR TREATMENT OF PERTUSSIS. K. OKUTANI, Japan J. Infect. Dis. **2**:957 (June 20) 1928.

Okutani made injections of from 10 to 15 cc. of 5 per cent emulsion of ether rectally through a soft rubber catheter, after the rectum had been cleansed with a glycerin enema. This was repeated once or twice daily, according to the severity of the symptoms. Of 104 patients thus treated, the paroxysm was controlled in 84.59 per cent, the percentage of effectiveness increasing with the age of the patients. The author considers that, clinically, ether given by rectum is an effective therapeutic method.

EFFECT OF ULTRAVIOLET RAYS ON DIPHTHERIA TOXIN. TETSURO SHINDO, J. Pediat. (Tokyo), March 20, 1928, no. 334, p. 496.

The author made a systematic study of the effect of ultraviolet irradiation on diphtheria toxin. The toxin in both liquid and dried forms was irradiated for a certain length of time, with the untreated toxin used as a control. He found that the toxicity was completely removed by irradiation with a Hanovia quartz lamp for thirty minutes at 4.5 cm., or for ninety minutes at 10 cm. As further proof of this loss of toxicity, guinea-pigs which had received injections of the minimal lethal dose died usually in from three to four days if the injections consisted of untreated diphtheria toxin but survived throughout the period of observation (thirty-three days) if they received injections of toxin which had been irradiated previously for ninety minutes. It was further found that when injections of irradiated toxin were made into the subarachnoid space in rabbits, the rectal temperature reached 40.4 C., while untreated toxin gave a temperature of 41.5 C. The cell count of the spinal fluid varied only a little and the appearance of paralysis was greatly delayed when injections were made with irradiated toxin. The author did not find changes in the hydrogen ion concentration of toxin whether it was irradiated or untreated.

DIET IN CHILDREN WITH TYPHOID FEVER. KAORU KAZAMATSURI, J. Pediat. (Tokyo), Sept. 20, 1928, no. 340, p. 1572.

Twenty young patients whose condition was diagnosed definitely as typhoid were fed with solid and semisolid food, adequate caloric values being aimed at in each case. The chief articles of food employed were: cow's milk with the addition of 5 per cent sugar, rice gruel, buttered toast or other bread, sugar or jam, eggs, fish, chicken meat, vegetable pureé confectionery, including sponge cake, chocolate and wafers, and fruits including peaches, pears, grapes, watermelons and oranges. In addition to the foregoing, noodles, bean curds and ice cream were given. The purpose was to give at least 30 calories of food per kilogram of body weight. Intestinal hemorrhage was not recorded in a single instance. The average period of fever was 19.3 days. All patients progressed to uneventful recovery.

KATO, Los Angeles.

Chronic Infections

PULMONARY TUBERCULOSIS, JUVENILE TYPE, AS RELATED TO TUBERCULOGENESIS. COLE B. GIBSON, M. J. & Rec. **128**:130 and 165 (Aug. 1 and Aug. 15) 1928.

From autopsies on children who died from various conditions, it has been shown that when the primary focus of tuberculous infection is in the lung, the regional lymph nodes are invariably involved, and also that by progression through the lymphatics and the blood stream general diffusion of the disease may occur. Three types of pulmonary tuberculosis in children may occur, viz., the infantile type, the juvenile type and the adult type. The first type includes the diffuse and widespread tuberculous infiltration seen in infants and young children. The juvenile type covers such descriptions as hilum tuberculosis, peribronchial tuberculosis or tracheobronchial tuberculosis. The circumscribed type of tuberculous lesion in the parenchyma of the lung, seen most often in adolescents and adults, does occur in children below the age of 12 frequently enough to warrant attention.

Latent tuberculosis gives morbid changes of a tuberculous character unaccompanied by signs or symptoms evident to the patient or physician. This type is in particular need of a proper classification of lesions. In the opinion of the author, children who react positively to tuberculin and who present roentgen evidence of abnormality of the hilum or parenchymal foci of infection unaccompanied by physical signs are rightly classified as having latent tuberculosis.

The most satisfactory way of applying the tuberculin test is the Mantoux method. The article is accompanied by roentgenograms of the lungs showing various tuberculous foci.

No symptom complex that occurs with this disease exclusively can be accorded the quality of pathognomonic. Moreover, the symptoms that do occur are seen often as the results of other diseases. The borderline between latent and manifest disease is often hazy and indeterminate, and diagnosis is largely a matter of exclusion. While children who have manifest juvenile tuberculosis may be underweight, others may be normal in weight or even above normal weight.

Physical as well as roentgen examination, together with the symptoms, help in diagnosis. To stigmatize a child as tuberculous when he is not is to impose a burden on his parents and on himself. And, on the other hand, in the absence of a specific against tuberculosis, further reduction in the death rate of the disease can be attained by more extensive prophylactic work.

When latent tuberculosis is discovered, the subsequent observation and proper handling of the children will ultimately result in the lessening of the number who develop manifest disease. Usually, manifest juvenile tuberculosis is amenable to treatment. If treatment cannot be carried on in the home, the patient should receive routine care in a sanatorium. Children with latent disease should be under continued or periodic observation.

WILLIAMSON, New Orleans.

THE EVOLUTION OF TUBERCULOUS INFECTION IN CHILDHOOD. OBSERVATIONS ON CHILDREN ADMITTED TO A DISPENSARY OVER A PERIOD OF TWELVE YEARS. CHARLES R. AUSTRIAN, Tubercle **9**:229, 1928.

A study of a group of persons observed at intervals through a period of from eight to twelve years demonstrates that though the maximum opportunity for tuberculous infection of the child is present in the homes of the actively tuberculous, extradomiciliary and extramural foci are also important sources of early contamination. Variations of response to the Pirquet test indicate the tuberculous infection may vary in degree from time to time, even when it has been acquired in earliest childhood. Roentgenographic evidences of moderate enlargement of the mediastinum, of slight fibrosis of the lungs or of old localized infiltration of the base of the lung may remain unaltered through a period of years, even when they are present in young children who react positively to the Pirquet test. The number of young persons exposed to the risk of tuberculous infection who will develop clinical tuberculosis is relatively small, if contact with the source of infection is removed, and good conditions of hygiene and diet are established.

H. J. CORPER.

INFANT VACCINATION WITH B. C. G. WEILL-HALLE and TURPIN, Arch. de méd. d. enf. **31**:517, 1928.

In an extensive contribution, Weill-Halle and Turpin confirm their observations in a previous study of four years' duration with Calmette's method of immunization against tuberculosis at the threshold of life. From 1921 to 1924, their experimental and clinical work involved only the first method proposed, that of ingestion, but for the succeeding five years, both procedures, ingestion and subcutaneous inoculation, were employed and their results compared. A total of 636 infants were immunized during this period, 23 by inoculation and 613 through the digestive tract. Prior to immunization, each infant remained under rigid observation for four weeks; exhaustive clinical examinations were made and cutaneous tuberculin reactions noted. If the infant was free from tuberculous infection, inoculation of from $\frac{1}{100}$ to $\frac{1}{50}$ mg. of the vaccine was given in the infraspinous fossa, this amount representing about 2,500,000 bacilli. Practically no serious constitutional disturbances followed these inoculations; between the thirty-fifth and the fortieth day, the small subcutaneous nodule which appeared at the site of injection at about the third week was converted into a cold abscess. This began to evacuate about the eighth week, at first discharging a small amount of thick, ropy pus which soon changed to a serous oozing that tended to persist for two or three months. The fistula dried up spontaneously, leaving a scar slightly adherent to the deeper tissues. In the early stages of this evolution, there was a tendency toward involvement of the adjacent lymph glands.

Of the twenty-three infants vaccinated, three are now 4 years of age; two are 3 years old, and five 2 years. Of the ten infants who were vaccinated in 1927-1928, three are dead. The first of these, vaccinated in 1924 in Paris, was cared for by a wetnurse and died at the age of 2 months in Brittany, of a type of meningitis not specified. The second fatality was that of an infant aged 17 months, previously in good health, who succumbed to an attack of measles complicated by bronchopneumonia. The third case was that of an infant who was vaccinated at 3 months of age, dying ten months later, after indifferent care, from some convulsive seizure of unknown origin. The remaining twenty children are in excellent health. Reference is made to similar experiences noted by Arvid Wallgren of Göttenborg and by Heimbeck of Oslo, the latter immunizing a number of nurses on duty at a municipal hospital for tuberculosis.

In the cases of Weill-Halle and Turpin, regular contact was maintained through the services of visiting nurses. Of the 613 persons immunized by ingestion since 1921, forty-one died from various causes, a mortality of 6.68 per cent. The conclusions reached from this series are of interest as interpreting the current views of French investigators.

1. Antituberculous immunization with B. C. G. in subjects free from previous infection is absolutely free of danger.

2. It can be accomplished either through the digestive route during the first ten days of life or by the subcutaneous method after this period.

3. If oral administration is employed, the new-born infant is given three doses of 1 cg. of B. C. G. according to indications furnished by the Calmette laboratory at the Pasteur Institute. This should be repeated at the age of 1 year and again at the age of 3 years.

4. In the subcutaneous method, the dose should vary from 0.01 to 0.5 mg., the average being about 0.02 mg. which represents about 800,000 bacteria.

5. The subcutaneous method of inoculation should always be preceded by a period of observation in which at least two negative reactions to the tuberculin skin tests at intervals of eight days are obtained.

6. It is also desirable to isolate these infants completely to avoid all contamination during the period of immunization.

7. The results of these observations, extending over six years and fortified by similar reports from various medical centers not only of France but of many other countries, prompt the authors to recommend the employment of this method in all infants whose surroundings are a menace; to those not endangered but whose parents desire them to be immunized, and to the personnel of hospitals for the treatment of tuberculous patients.

AMESSE, Denver.

THE DIAGNOSIS AND PROGNOSIS OF PRIMARY PULMONARY TUBERCULOSIS IN THE INFANT. E. RIST AND J. LEVESQUE, Rev. franç. de pediat. **4**:271, 1928.

This study of pulmonary tuberculosis in the infant is given over largely to the interpretation of roentgen examinations. Thirty-four plates show the observations in eighteen cases, seven of which were checked by autopsy. In the first group of eleven cases the first x-ray pictures showed shadows about the hilum in the region of the heart, such as are ordinarily taken to indicate enlarged tracheobronchial lymph glands. Later x-ray pictures showed that in all instances these shadows had become much less or had disappeared, clinical improvement occurring coincidently. In the other group of seven cases, the shadow was situated along the trachea above the bifurcation. All of these patients died, showing either miliary tuberculosis, tuberculous meningitis or tuberculous bronchopneumonia. Postmortem examination showed the shadow along the trachea to be due to large caseating glands. Because of the frequency with which large caseating glands are associated with generalized tuberculosis and because of the rapidity with which the shadows about the hilum disappeared in the first group of cases, the authors feel that in most instances shadows about the hilum are due not so much to enlarged glands but to the reaction of the parenchyma of the lung itself to the tuberculous infection. Thus, shadows about the hilum offer a much more favorable prognosis than those occurring along the trachea.

BILATERAL PNEUMOTHORAX IN THE CHILD. P. GAUTIER, Rev. franç. de pediat. **4**:358, 1928.

Two cases of bilateral caseous pulmonary tuberculosis in children, aged from 7 to 8 years, are reported. Pneumothorax was first practiced on one side only, but as the lesions on the opposite side were seen to be progressing unfavorably, bilateral treatment was instituted. The injections of air were made about every week, the sides being alternated. The amount injected varied with the size of the patient, the terminal pressure being kept negative. As improvement took place, the interval was lengthened. The children showed little respiratory embarrassment, although x-ray pictures showed that the lungs were collapsed to a considerable degree. They became afebrile, put on weight, and later x-ray pictures showed a marked improvement in the lungs. It is well to institute treatment early, before the formation of pleural adhesions. The author feels that this treatment is of great value and involves little risk.

LESLIE, Evanston, Ill.

THE VALUE OF WILDBOLZ' REACTION IN CHILDREN. GIUSEPPINA URBANI, Riv. di clin. pediat. **26**:532, 1928.

Wildbolz (*Schweiz. med. Wchnschr.* **50**:32, 1919) reported the observation of an antigen in the blood and urine of patients with tuberculosis; the intracutaneous injection of their urine concentrated to 1/10 volume caused an infiltration of the skin identical with that obtained with the intracutaneous tuberculin test.

The author has experimented with forty-four children, some tuberculous and some not, comparing the Wildbolz test with the tuberculin test. Her conclusions are: 1. There is no parallelism between the autoreaction and the cutaneous tuberculin reaction. 2. The reaction of Wildbolz is not due to the elimination of the specific antigen and therefore is not an expression of an active or latent tuberculous focus. 3. On the contrary, it is related to the urinary salts and colloids, and one cannot attribute to it any diagnostic and prognostic value.

HIGGINS, Boston.

THE TECHNIC OF EXAMINATION FOR SPIROCHETES IN INFANTS. F. WEISS, Arch. f. Kinderh. **84**:279 (July 20) 1928.

The author gives further results of his success in the examination of nasal and conjunctival secretions for spirochetes. The results reported in the first article (*Arch. f. Kinderh.* **83**:68 [Jan. 5] 1928) seem to justify this examination as a valuable diagnostic aid in the differentiation between exanthems with conjunctivitis and a specific syphilitic infection.

SANFORD, Chicago.

TRANSVERSE METAPHYSEAL BAND SHADOWS IN ROENTGENOGRAMS OF CHILDREN WITH TUBERCULOUS ARTHRITIS. OTTO WIESE, Beitr. z. klin. Chir. **142**:428, 1928.

Certain definite transverse band shadows were noted by the author in the metaphyseal ends of the femur and tibia in the involved as well as the uninvolved knee joint. He found these band shadows most pronounced in the metaphyses of the knee joint, slightly less marked in the wrist joints and ankle joints and not visible in the regions of the shoulder, elbow and hip joints.

It was observed that as soon as these children started walking these shadows tended to disappear. A definite etiologic factor was not offered. The author suggested, however, that in all likelihood the shadows were the result of the disturbed deposition of calcium. He saw similar but much less distinct shadows in children with rickets.

OBERHELMAN, Chicago.

TUBERCULOSIS OF THE SPLEEN AND ITS DEMONSTRATION BY THE X-RAY: A CONTRIBUTION TO THE KNOWLEDGE OF THE HEMATOGENOUS EXTENSION OF TUBERCULOSIS IN CHILDHOOD. W. COURTIN and J. DUKEN, Ztschr. f. Kinderh. **45**:603 (June) 1928.

Courtin and Duken report four cases of tuberculosis of the spleen. In three patients they successfully demonstrated with the x-ray, for the first time, the calcification of the spleen due to an extension of tuberculosis through the blood stream from foci in the lungs, mesentery and liver. In the fourth case autopsy disclosed a caseous spleen with the formation of a cavity. Signs of uremia appeared at the time of death. These followed nephritis which had occurred secondary to a sore throat. The spread of this infection could be attributed possibly to the impaired action of the spleen.

TYPES OF ACUTE HEMATOGENOUS PULMONARY TUBERCULOSIS IN CHILDHOOD (MILIARY INVASION OF THE LUNGS). W. DEUL, Ztschr. f. Kinderh. **45**:615 (June) 1928.

Deul remarks with what few signs hematogenous pulmonary tuberculosis may occur. The scanty clinical evidence and the slight influence on general conditions unfortunately are thought to indicate grip. If the characteristic fever, often

observed by Deul, exists, the sick child should be examined further, especially by the x-ray, despite the cessation of the first subjective symptoms; further, a hematogenous pulmonary tuberculosis should be suspected, even if the tuberculin reaction at first is negative. The temperature is uneven; its subfebrile course is broken for days by strong remissions, with a rise in temperature to 103 F. in the evening. After years of study, the investigator obtained some idea of the courses which pulmonary tuberculosis may run. He showed the manifold character of the disease which either leads quickly to an unexpected recovery or to forms of termination which resemble those of tuberculosis in adults. There may be: (1) a quick course ending in death from general miliary tuberculosis and meningitis; (2) transition from a similar severe form to a prolonged stage of quiescence with subjective well being which points toward an unconditional and swift lethal ending, or (3) in connection with such a quiescent period, a transition on the one hand to progression and on the other to calcification and cessation of the disease.

EMERSON, Boston.

RESULT OF TREATMENT OF CONGENITAL SYPHILIS AND BLOOD GROUPING. P. KISS and F. SKROP, Orvosi hetil. **72**:203, 1928.

The authors compared the results of antisyphilitic treatment of children in the different blood groups. Verzár's method was used as a basis for classification. The blood groups are designated O, A, B and AB. Group O is not agglutinated by any of the other groups; A is agglutinated by B; B by A, and AB by all the other three. The report includes 114 children, 40 of which belong to group O, 50 to group A, 13 to group B, and 9 to group AB. The results are as follows: The Wassermann reaction became negative in the shortest time in children of group O, and in the longest time in those of group AB. The return to a positive Wassermann reaction after apparent success of the treatment occurred in the highest percentage among children of group AB, and in the lowest percentage among those of groups O and A. The Wassermann-fast cases were practically all of group AB. Almost all the children showing continuous negative reactions to the Wassermann test over a period of two years belong to group B; only a few were in group AB. It seems that children of group AB give the least favorable results in the treatment for congenital syphilis.

DEEP X-RAY THERAPY IN CERTAIN CASES OF TUBERCULOSIS OF THE LUNGS. Z. BOKAY, Orvosi hetil. **72**:825, 1928.

In twenty-nine children with hilum tuberculosis and beginning infiltration of the lungs, deep x-ray therapy was used at intervals of four weeks; altogether, from three to five treatments were given. The author thinks that this form of treatment is without danger and that the results are satisfactory. The processes in the hilum seem to be affected most beneficially by this therapy. Cases showing infiltration of the lungs are less responsive to treatment, and only beginning forms of so-called epituberculous infiltration should be selected. The fact that the treatment takes only a short time has a great social significance.

ZENTAY, St. Louis.

Internal Diseases

ENURESIS IN CHILDREN. JOSEPH K. CALVIN, M. Clin. N. Amer. **12**:131 (July) 1928.

With efficient parental cooperation, the average physician, in most cases, can easily and successfully combat enuresis in children. Two groups of cases are encountered: In the smaller, comprising about one third of the cases, there is an underlying organic or physical basis, such as diabetes insipidus, mental deficiency, vaginitis and cystitis or chronic interstitial nephritis. The prognosis and treatment in this group are determined by the physical factor. In the larger group, it is due to the formation of bad habits, either from lack of proper training, or from overstimulation of the nervous system, or both.

Results in this group depend largely on the confidence of the physician in his ability to handle the case successfully and on his ability to communicate this confidence to the child. Special psychopathic treatment is seldom necessary. Mothers are directed to stop all punishment, shaming, arguing and all emotional displays, and to stimulate in the child a confidence in his power to control the condition. Rewards are more effective than punishment. The usual restrictions of diet and liquids are imposed. Rest and avoidance of excitement are enjoined. The child is required to empty the bladder on retiring and again at 10 or 11 p. m. Awakening the child at other times during the night seems rather to fix the habit than to correct it. Interrupted urination during the day for purpose of training causes the child to concentrate on his difficulties.

The author considers that treatment with drugs is of major importance in hastening a cure. Phenobarbital raises the threshold of the nervous response and is valuable in the high-tensioned child. Atropine relaxes the smooth muscle fibers of the bladder and increases the capacity to hold fluid. In obstinate cases, such as those in noncooperative older children, removal to a hospital or another suitable institution will usually bring about a permanent cure within a few weeks.

SMITH, Ogden, Utah.

THE PRERHEUMATIC CHILD. C. WILFRED VINING, M. J. & Rec. **127**:351 (Oct. 3) 1928; **128**:453 (Nov. 17) 1928.

In his papers the author showed that the majority of children who develop clinical rheumatism with or without cardiac disease have a period of defective health for months or years preceding the first attack. A detailed analysis of symptoms is given, which shows that toxemia and a disorder of the alimentary tract exist. This prerheumatic debility is similar to the debility of the so-called toxic debilitated children who attend the childrens' outpatient departments in such large numbers.

The evidence given shows that the majority of rheumatic children and children with toxic debility have enlarged tonsils and unhealthy throats. In only 18 of 205 cases was sore throat coincident with the initial attack.

Reference is made to the work of McCarrison in connection with pigeons and monkeys fed with diets lacking vitamin B, and comparison is invited between the symptoms he recorded and the symptoms of many of the children with toxic debility.

The conclusions drawn from the study are: Rheumatism of childhood is primarily a disease based on nutritional disturbance brought about by a prolonged dietetic deficiency either in vitamin B or in protein in conjunction with a relative excess of carbohydrate, or possibly to both of these factors. Although the brunt of the defect appears to fall on the alimentary tract, the results are widespread and produce loss of tone in all the systems, especially the mucous, lymphatic, nervous and muscular.

Secondarily, rheumatism is an infection caused by a streptococcus which passes in through the weakened lines of defense, and in this way the toxemic element of the debility is produced.

The number of cases of rheumatism occurring in a district is in proportion to the number of children with toxic debility existing in that district. The success of one's efforts to prevent and control rheumatism will be in proportion to the amount of recognition that is given to the prerheumatic health defect, and prevention lies first and foremost in the provision of a well-balanced diet from infancy.

WILLIAMSON, New Orleans.

AGRANULOCYTOSIS: CASE REPORT. D. M. DAYTON, Northwest Med. **27**:436, 1928.

Dayton reports a case of agranulocytosis in a girl, aged 7. There was a sudden onset with sore throat, fever, prostration and swelling of the anterior cervical glands. On the third day, a hemorrhagic gingivitis developed. On the fourth day, severe hemorrhages from the nose occurred. The tonsils and gums became

necrotic and gangrenous despite frequently repeated transfusions. A few petechial spots appeared on the skin. The patient died on the tenth day. The first blood count showed 600 leukocytes, only 2 per cent of which were polymorphonuclears. No count showed more than 2,500. Platelets varied between 50,000 and 100,000, and the coagulation time was three minutes. The bleeding time was from nine minutes to several hours. Cultures from the throat showed nothing of significance. Blood culture just before death showed *Streptococcus viridans*. Necropsy showed enlarged inflamed tracheobronchial glands. The bone marrow was composed almost entirely of fatty tissue and showed little cellular structure. The granular cells were absent. Dayton comments on the frequency of reports of this condition and compares it to acute leukemia, monocytic angina and acute aplastic anemia.

SCOTT, Philadelphia.

THE THYROID GLAND AND COMMUNICABLE DISEASES: IMMEDIATE AND REMOTE EFFECTS OF COMMUNICABLE DISEASES UPON THE THYROID GLANDS OF ELEMENTARY SCHOOL CHILDREN IN CINCINNATI. ROBERT OLESEN, Pub. Health Rep. **43**:3009 (Nov. 16) 1928.

There is evidence that one of the immediate effects of communicable diseases among girls of elementary school age is a simple enlargement of the thyroid gland. This enlargement, however, appears to be temporary in character. A comparatively short time, as yet undetermined, after a child recovers from a communicable disease, he is not any more prone to changes in the size of the thyroid than a child who has not had a communicable disease.

As far as children in the elementary school are concerned, there does not appear to be any ground for assuming that the ordinary communicable diseases are responsible for the growth of simple goiter. The underlying causes of this malady must be sought in other directions.

SANFORD, Chicago.

GIARDIASIS IN CHILDREN. JOHN ZAHORSKY, South. M. J. **21**:595, 1928.

Giardia intestinalis is found frequently in the feces of children and infants. Older children frequently are infected but do not manifest any digestive or nutritional disturbances.

In infants the parasite produces increased intestinal peristalsis, a lessening in the absorption of food and a consequent retardation of growth.

The use of bismuth salicylate several times a day for a week, repeated several times during a period of six months or more, improves the clinical condition and may remove the parasite.

CHOLECYSTITIS AND CHOLELITHIASIS IN CHILDREN. J. A. BEALS, South. M. J. **21**:672, 1928.

Cholecystitis and cholelithiasis occur more frequently in children than is commonly supposed. In addition to a case under his observation, in a child aged 3 years who showed gallstones, the author collected reports of 124 cases from the literature.

These fall into three groups: those showing gallstones in early infancy, those showing gallstones in later infancy and those manifesting acute cholelithiasis.

The author recommends more careful roentgenologic search for these disorders.

INVESTIGATION OF HOOKWORM CONDITIONS AMONG PUPILS FROM SIX TO TEN YEARS OF AGE IN FOUR SCHOOL DISTRICTS IN DECATUR COUNTY, GEORGIA. M. A. FORT, South. M. J. **21**:917, 1928.

Hookworm disease is still a serious menace in a large part of Georgia and other southern states, particularly in those areas having a predominantly sandy loam.

Fewer than fifty hookworms can produce changes in the blood picture of the child; these changes do not disappear immediately when the hookworms are removed. A high eosinophil count persists long after treatment. Toxins excreted by hookworms apparently affect the normal blood regenerative functions. These functions may be impaired for years and certainly remain so long after treatment.

The mixed treatment recommended by Smillie and Pessoa (Bull. Int. Health Board, January, 1923, 191) is successful and practical.

SCHLUTZ, Minneapolis.

FAMILIAL CASES OF HYPERTROPHIC PYLORIC STENOSIS. E. A. COCKAYNE, M. A. MONCRIEFF and W. P. H. SHELDON, Proc. Roy. Soc. Med. **20**:1261 (May) 1928.

The authors gave the history of a family in which three of five children had suffered from pyloric stenosis. In two, the diagnosis was confirmed at operation; the third suffered from all the symptoms but did not undergo an operation. He was treated medically, and a cure resulted.

HYPERTROPHIC PYLORIC STENOSIS IN UNIOVULAR TWINS. D. R. HUTCHINSON, Proc. Roy. Soc. Med. **20**:1261 (May) 1928.

The patient was a twin and was admitted to the hospital at the age of 5 weeks on account of vomiting. The diagnosis of hypertrophic pyloric stenosis was made. Rammstedt's operation was performed, and uneventful recovery ensued. Symptoms began in the other twin at the age of 3 weeks; he was operated on, but died six days after operation. He weighed 1 pound (453.6 Gm.) less than the first patient. The attending midwife reported that there was one placenta, one chorion and two amniotic sacs.

CARCINOMA OF THE SUPRARENAL. G. E. NELIGAN, Proc. Roy. Soc. Med. **21**:1321 (June) 1928.

For about six months the mother of a girl, aged 5 years, had noticed an increase in the size of the child's abdomen. The child had complained occasionally of pain in the abdomen. She had appeared to be growing up rather rapidly. When first seen she seemed several years older than her years. There was a hard, fixed tumor in the left side. The liver was not enlarged. The pubic hair was well developed. Laparotomy was done, and a tumor was found fixed to the posterior abdominal wall and to the upper pole of the kidney. The tumor and kidney were removed, and the child made an uneventful recovery.

SECONDARY ANEMIA TREATED WITH LIVER DIET. A. G. MAITLAND-JONES, Proc. Roy. Soc. Med. **21**:1325 (June) 1928.

The author reports a case of secondary anemia in a child, aged 1 year, who showed signs of rickets. He gave her doses of iron and cod liver oil by mouth for two weeks, but the anemia was unimproved. He then gave doses of liver daily, and within two weeks the red blood cells and the hemoglobin were increased.

WILLIAMSON, New Orleans.

TOXI-INFECTIOUS HEPATITIS OF ACIDOTIC FORM IN THE INFANT. P. ROHMER and J. STOLZ, Rev. franç. de pediat. **4**:367, 1928.

Two cases are reported, one of which was considered to be dysentery and the other a disturbance of the choleriform type, in which a few days after the onset of the gastro-intestinal symptoms, there was sudden development of agitation, hyperpnea and fever, which passed rapidly into coma and death. In both instances the urine showed large amounts of acetone. The principal condition found post mortem in both cases was an acute toxic hepatitis resembling that found in phosphorus poisoning. The intestinal tract showed catarrhal inflammation, with marked lymphoid reaction. The authors consider the acidosis as an index of the destruction of the liver but not in itself responsible for the coma and death, which they suggest might be due to toxic products coming from the destruction of the liver cells.

LESLIE, Evanston, Ill.

EXUDATIVE DIATHESIS IN THE NURSLING. AMADOR TOLEDANO, Arch. españ. de pediat. **12**:477, 1928.

The author is of the opinion that this form of diathesis like all other forms is hereditary. It is manifest especially during the period of active growth, particularly during the nursing period.

Exclusive or preponderant feeding of milk is among the major causes which provoke to activity a latent exudative diathesis. Good results were not obtained with protein therapy in this condition.

A well regulated dietetic regimen with a small amount of milk, combined with suitable local treatment, has proved the most effective measure to relieve the condition.

SCHLUTZ, Minneapolis.

THE CAPILLARIES IN SOME NEPHROPATHIES OF CHILDREN. G. FRONTALI, Riv. di clin. pediat. **26**:81, 1928.

The author has studied the capillaries in diseases of the kidney for several years. He reports his conclusions from the examination of thirty-two children with different types of lesions of the kidney. He observes the microscopic appearance, the fragility and the blood pressure of the skin capillaries.

Such examinations permit: (*a*) differential diagnosis between certain types of glomerular nephritis (when vascular changes occur) and nephroses (when vascular changes do not occur); (*b*) early diagnosis of nephritis and thus early treatment and (*c*) selection of persons who are predisposed to vascular endothelial diseases and who should receive prophylactic care.

ANGINA PECTORIS IN A BOY: ITS FREQUENCY IN CHILDHOOD AND ADOLESCENCE. P. DOTTI, Riv. di clin. pediat. **26**:350, 1928.

A boy, aged 15 years, who worked as a barber, had rheumatic fever at the age of 3, and a recurrence shortly before the onset of the anginal attacks. The attacks were typical; they usually occurred at night and varied in intensity over a period of six months. He did not have attacks during the last three weeks of his life. He died of cardiac decompensation. A necropsy was not obtained.

CONGENITAL AND FAMILIAL LEUKEMIA. G. MACCIOTTA, Riv. di clin. pediat. **26**:440, 1928.

The author reports the occurrence of lymphatic leukemia in all five children of one family and in the last four of eight children in another family. Case reports of one child in the first family and of three in the second family are given. The disease appeared in infancy and was not related to syphilis, tuberculosis or other known infection.

FOOD ANEMIA FROM GOAT'S MILK. P. BARBACCI, Riv. di clin. pediat. **26**:489, 1928.

One case is reported of a child, aged 7 months, who was anemic; it had been fed wholly on a formula of goat's milk since the age of 8 days. The author believes that the blood picture tends to be like that of pernicious anemia.

HIGGINS, Boston.

EDEMA IN PATIENTS WITH EXOPHTHALMIC GOITER. MALTE LJUNGDAHL, Wien. Arch. f. inn. Med. **21**:1, 1928.

The author reports six cases of typical exophthalmic goiter which periodically exhibited extensive edema with ascitis and at times hydrothorax. Four of the cases also showed icterus.

These extensive edemas are seemingly not incompatible with a fairly good condition of the patient. They are probably largely the result of stasis produced by a heart insufficiency.

Of all the remedies used iodine had the most pronounced diuretic effect. The author is of the opinion that the occurrence of icterus in connection with exophthalmic goiter is not necessarily a serious symptom. It is probably also the result of a stasis.

SCHLUTZ, Minneapolis.

SEVERE INTESTINAL HEMORRHAGE FROM AN ULCER IN A MECKEL'S DIVERTICULUM. W. C. MEISS, Nederl. Tijdschr. v. Geneesk. **72**:4040, 1928.

The author presents a case in a child, aged 2 years. The child fell ill suddenly with abdominal symptoms, the principal symptom being a severe bloody diarrhea. The large amount of blood passed by stool was clear and red. An invagination was therefore improbable, but a tumor of the vagina could not be palpated. At the time the lapartotomy was performed, a Meckel's diverticulum, about 3 cm. in length, was found almost 50 cm. from the cecum, the top had perforated into the ileum at a point about 20 cm. higher. The child recovered.

Histologic examination showed that the mucosa of the diverticulum was for the most part three or four times thicker than the intestinal mucosa and resembled the gastric mucosa. At the free edge, the mucosa of the diverticulum had a defect covered with fibrin under which there was a large amount of granulation tissue; this was probably the place from which the bleeding had occurred. The peritoneum of the diverticulum also consisted of granulation tissue.

VAN CREVELD, Amsterdam.

Nervous Diseases

A STUDY OF THE PHYSICAL AND MENTAL CHARACTERS OF MONGOLS. IRA S. WILE and SAMUEL Z. ORGEL, Internat. Clin. **3**:145 (Sept.) 1928.

Twenty-five mongolian imbeciles were studied in detail, particularly as to their psychologic aspect. Congenital defects described were a brachycephalic skull, slant eyes, epicanthus, widely spaced eyes, a small nasopharynx due to a backward projecting vomer, a short, thick neck, a short spade hand, short, stubby feet, short extremities, coarse dry hair, dry skin, poor circulation, lobeless ears, prehensile toes, relaxed ligaments and a curved little finger. Less frequently noted characteristics were darwinian tubercled ears, a single line on the palm, nystagmus, strabismus, cryptorchidism, patent foramen ovale, mongolian spots and webbed toes. Deposits of fat, when present, disappeared with thyroid therapy.

Developmental defects which were present in all cases were a high arched palate, delayed eruption of teeth, faulty enamelization of teeth, rachitic changes, scrotal tongue, flat feet, delayed speech, delayed walking and delayed muscular development. Defects found less frequently were umbilical hernia, cardiac murmurs, scoliosis, exophthalmus and angioneurotic edema. Detailed psychologic tests place these children in the class of imbeciles instead of idiots.

The median age of parents of the mongol group was ten years higher than the average normal age for both fathers and mothers. The age at which the parents were married was higher than in the normal group. Only six of the mongols were the last born of large families. Many theories of etiology, such as fetal arrest of development and the use of contraceptives, are discussed.

MILLER, South Bend, Ind.

BEHAVIOR DISTURBANCES IN CHILDREN. RALPH C. HAMILL, M. Clin. N. Amer. **12**:111 (July) 1928.

The egoism of children is easily hurt and can be counted on to make the hurts known. Forcing this ego to conform to a certain pattern and adjusting it to social conventions may become a painful process. Resentment and anger are often the reactions to forced adjustment; when the subjects encounter a degree of superiority against which they can make no impression, fear results. Resentment and anger plus impotence and discouragement produce fear. This formula covers the emotional elements of maladjustment, disturbances in behavior, mental disease, the psychoneuroses and the psychoses. These emotions lead to action but seldom to straight thinking.

Difficulties of behavior in children are of the same type as psychotic or insane behavior in adults. Both are attempts at instinctive expression which is not trimmed and molded to the conventional forms. The essential difference lies in the field of the imagination: The bad boy misbehaves to attract attention; the person with paranoid praecox knows that every one is looking at him. Both allow their egoism free rein at the expense of others instead of adjusting themselves to others. It seems that there are two important elements behind all difficulties of behavior; these are fear and rebellion. In the child they manifest themselves in such activities as restlessness and inattention, poor sleep and night terrors, enuresis and self soiling, tantrums and breath holding, capricious appetite and vomiting. Drugs and opiates are not indicated in the treatment for such conditions; rather, the elements of fear and rebellion are sought out and dealt with directly. In the histories of numerous cases, the author discusses the underlying causes and rational management of these maladjustments.

SMITH, Ogden, Utah.

MINOR NEUROSES OF CHILDHOOD. J. EPSTEIN, M. J. & Rec. **128**:354 (Oct. 3) 1928.

Mental processes of the young child are under feeble control and coordination, and added to this imperfect condition an inherited weak, unstable nervous mechanism often exists. These children who suffer from neuroses may live amid unfavorable surroundings and frequently suffer from functional disorders of all kinds. These minor neuroses may be divided into mental or physical, internal or external. The physical neuroses may manifest themselves as gastro-intestinal, respiratory, cardiovascular or urinary spasmodic disorders. Cerebral spasms, psychic disorders and depraved habits are frequently due to an unstable psychoneural juvenile system. An early diagnosis is essential to proper therapeutics. Treatment consists, mainly, in improving the body and reconstructing the mind — by good food, healthful, physical and mental surroundings, proper drugs and suitable hydrotherapeutic measures.

WILLIAMSON, New Orleans.

THE CHLORIDE, SUGAR AND CALCIUM CONTENT OF THE CEREBROSPINAL FLUID. A. V. NEALE and M. S. ESSLEMONT, Arch. Dis. Childhood **3**:243 (Oct.) 1928.

The spinal fluid was studied in children less than 2 years of age. The sugar, chloride and calcium were found to be essentially normal in children suffering from various diseases with meningeal involvement. In tuberculous meningitis a constant low chloride content was not found, and the sugar was not low. In fatal meningococcic and pneumococcic meningitis, there was a progressive diminution in the sugar content. A calcium deficiency was not found in patients with convulsions.

PETERMAN, Milwaukee.

CASE FOR DIAGNOSIS. A. G. MAITLAND-JONES, Proc. Roy. Soc. Med. **21**:1325 (June) 1928.

The author reports a case of convulsions in a child, aged 11 months. The infant was born at full-term, and the labor was normal. At the age of 4 months it began to have convulsions which continued at frequent intervals. The fits consisted of jerking movements of the limbs and rolling of the eyes. The child was blind and mentally defective. There was a slight spasticity of the lower limbs and optic atrophy. The cerebrospinal fluid was normal. The Wassermann reaction was negative. Roentgen examination of the skull gave negative results.

CEREBRAL ABSCESS. HUGH CAIRNS, Proc. Roy. Soc. Med. **21**:1329 (June) 1928.

For four weeks before he was seen by the author, the patient, aged 7 years, had been subject to jacksonian fits in the left side of the face, headache and

vomiting. At operation an abscess was found beneath the "face area" of the motor cortex and the adjacent part of the postcentral gyrus. The abscess was drained, and the child did well.

As to the cause of the abscess, evidence of infection from the ears, sinuses or mastoid processes could not be found. Pus yielded a pure culture of *Staphylococcus aureus*. The child had had an infected knee a few weeks before the symptoms began. A few days after operation, a pustule on the finger gave a culture of *Staphylococcus aureus*. The author thinks that the abscess was of metastatic type and that the infection entered the body through the cut on the knee.

WILLIAMSON, New Orleans.

ACTION OF THE ULTRAVIOLET RAYS ON THE VEGETATIVE NERVOUS SYSTEM. LUCIEN GAROT, Rev. franç. de pediat. **4**:318, 1928.

The author calls attention to the numerous free nerve endings near the epidermis which might be influenced by ultraviolet irradiation. He conceives the possibility that ultraviolet irradiation, by stimulating the nerve endings and acting reflexly, might change the tonus of the vegetative nervous system. When the oculocardiac reflex in ten children was determined before and after irradiation, pressure on the eyeball was found to be less effective in decreasing the heart rate after irradiation than before. Since this reflex operates through the vagus, the tone of the vagus is thought to be lessened. The change in heart rate following the administration of atropine was also studied. After irradiation for ten minutes, the increased rate due supposedly to paralysis of the vagal endings by atropine was found to be less than that before treatment. This condition disappeared in from twenty-four to forty-eight hours, but after a series of irradiations the increase in rate following the administration of atropine was persistently less than before any irradiation had been given. The effects of irradiation on the blood pressure were not noted. The author is convinced that the reflex establishment of a parasympathetic hypotonicity with a corresponding predominance of sympathetic action must be considered among the beneficial effects of ultraviolet irradiation. His presentation would be more convincing if control experiments had been cited.

LESLIE, Evanston, Ill.

PARKINSON'S DISEASE IN A CHILD AGED 6 YEARS. MARTINEZ VARGAS, Arch. españ. de pediat. **12**:257, 1928.

The author reports a case of Parkinson's disease which developed in a child at the age of 6 years. The patient is now 13 years old. Results of Wassermann tests of both spinal fluid and blood have been consistently negative. At the age of 3, the child had some form of cerebral inflammation probably in the nature of encephalitis. The actual tremors and symptoms of paralysis agitans did not begin before the age of 6; they started in the right hand and arm and rapidly spread to all the extremities.

At the age of 13, the child presented a classic picture of paralysis agitans. The mentality of the child was good although education had been neglected completely.

Every form of therapy tried was ineffectual in either ameliorating or improving the condition or in any way staying the progress of the disease.

CEREBROSPINAL MENINGITIS. LUIS MORQUIO, Arch. españ. de pediat. **12**:447, 1928.

This Latin-American clinician sums up the treatment of cerebrospinal meningitis and recommends the injection of an antimeningococcic serum as early as possible. In general, it should be given intraspinally. It may also be given intramuscularly, but the author seldom gives it intravenously. The injection of serum must be repeated for a number of successive days. It is seldom necessary to give more than five or six injections.

The author has observed cases in which a relapse of the condition followed the cessation of the injections. In such cases it is necessary to desensitize the patient and repeat the series of injections. Even in these cases, the results are generally satisfactory.

SCHLUTZ, Minneapolis.

PERMEABILITY OF THE MENINGES. S. ROSENBAUM, Monatschr. f. Kinderh. **40**:303, 1928.

A review of the subject takes up anatomic considerations and a discussion of the location and method of the formation of the cerebrospinal fluid. Permeability of the meninges varies even without disease, for instance, during menstruation or the last half of pregnancy. A great number of diseases, of course, cause increased permeability, both general and local. Pneumonia seems to cause a general increase, while meningitis and syphilis may cause local changes in permeability. Certain drugs, alcohol and arsenic, for example, cause a diminished permeability.

Abnormal permeability is useful in diagnosis, as an increase of calcium occurs in cerebrospinal syphilis, of dextrose in encephalitis and poliomyelitis and of chlorine in uremia.

GERSTLEY, Chicago.

REPORTS OF TWO HUNDRED AND FORTY-EIGHT CASES OF MENINGITIS. J. C. SCHIPPERS and H. J. PETERS, Nederl. Tijdschr. v. Geneesk. **72**:3685, 1928.

One hundred and eighty-seven of the 248 cases of meningitis about which some statistics are given in this article were cases of tuberculous meningitis, 37 of cerebrospinal meningitis and 24 of pneumococcic meningitis.

The tuberculous meningitis occurred somewhat more frequently in girls than in boys. The greater number of these patients were under the age of 3 years. The cases occurred most frequently in the last part of the winter and in the spring, though the well known spring peak was not marked. In seven cases the disease was preceded by acute otitis media and in two cases by acute mastoiditis. One of the patients recovered.

The cases of epidemic cerebrospinal meningitis occurred for the most part in boys (twenty-five against twelve in girls), and twenty-three of the thirty-seven cases were in infants. The mortality for infants was much larger than for older children, and for boys than for girls. Most cases occurred in January. The authors believed that injections of antimeningococcic serum had a beneficial effect in treatment, if the injections consisting of sufficient amounts were given early in the illness. They emphasized the fact that meningococcic meningitis in infants often gives few symptoms.

In an after investigation it was found that fourteen of the thirty-seven patients remained alive of whom nine recovered totally, two were partly invalided, whereas three were idiotic.

The greater number of the twenty-four cases of pneumococcic meningitis occurred in very young children. The influence of age, sex and season was not obvious in these cases. Most cases occurred during the first half year of life. The disease occurred as often spontaneously as after already existing diseases of other organs, especially after pneumonia. In one case acute nephritis was also present. The treatment consisted in lumbar punctures, and also in some cases in the injection of antipneumococcic serum. The after investigation of the six patients cured showed that three remained alive, were in the best of health and were normal. These three patients are the only three of all the twenty-three treated who recovered completely, so that the authors conclude that the prognosis "quoad restitutionem ad integrum" is fairly bad.

SEVERAL FORMS OF CURABLE MENINGITIS AND ENCEPHALITIS. E. GORTER, Nederl. Tijdschr. v. Geneesk. **72**:4489, 1928.

In this article the author gives several examples of curable forms of meningitis and encephalitis, which have been seen more frequently in recent years. Their

recognition as benign conditions is usually difficult, especially in the first days of the illness. The author illustrates this by interesting examples of these forms of acute meningo-encephalitis. The first case appeared after epidemic parotitis and the second after chickenpox; in the third case the etiology was obscure, but the illness was complicated by nephritis, and the fourth example was a case of post-vaccinal encephalitis.

The curable forms of meningitis may resemble closely beginning tuberculous meningitis. They must be distinguished from the so-called "meningisme" (Dupré), cases of meningeal irritation which may appear, i. e., after otitis media, pneumonia and typhoid, and in which the symptoms of meningitis are not so distinctly pronounced and which disappear quickly.

The forms of encephalitis which have a less hopeless course and which have been encountered more frequently in recent years, usually last a shorter time, but their recognition and distinction from the classic forms of encephalitis may be difficult. It is characteristic of this milder type of encephalitis for the meningeal symptoms to occur more frequently in it. In one case the symptoms of meningitis could not be found at the first examination, but that meningitis existed could be concluded from the presence of much albumin and many cells in the cerebrospinal fluid.

The author regards it as significant that these acute benign forms of meningitis, encephalitis and meningo-encephalitis occur in connection with a preceding disease, just as nephritis may appear after all kinds of acute infections. He thinks it improbable that the encephalitis is caused by an activation of a latent infection.

In the author's opinion a predisposition to anatomic disease of the nervous system is the reason that these complications occur in some persons much earlier than in others. The same may hold true for other diseases of the nervous system, also for tuberculous meningitis.

In regard to therapy, the author advises lumbar puncture not only for diagnostic purposes but as treatment which should be repeated every time the symptoms of the disease change for the worse.

VAN CREVELD, Amsterdam.

Diseases of the Eye

THE IMPORTANCE OF PHLYCTENULAR CONJUNCTIVITIS IN PEDIATRICS. MANUEL MARÍN AMAT, Arch. españ. de pediat. **12**:273, 1928.

Many factors are involved in the correct treatment for this important and common disease of the eye occurring during infancy and childhood. The hygienic, dietetic and medicinal treatment concerns the pediatrician more than it does the oculist. If successfully applied, it will always influence the condition of the eye favorably.

The author recommends carefully controlled tuberculin therapy for intractable cases. For the phlyctenular ulcers, mild mercurous chloride and yellow oxide of mercury are recommended. For the troublesome eczema about the palpebral fissures, the author uses Lassar's paste and a 3 per cent solution of silver nitrate. The essential consideration in the successful treatment for the condition is complete cooperation between pediatrician and ocultist.

SCHLUTZ, Minneapolis.

Diseases of the Ear, Nose and Throat

ETHMOIDITIS IN INFANTS AND IN YOUNG CHILDREN, WITH ACCOMPANYING EYE AND ORBITAL COMPLICATIONS. CLEMENT F. THEISEN, Arch. Otolaryng. **8**:386 (Oct.) 1928.

A general review and comment are given for thirty-one cases of ethmoiditis in children ranging in age from 6 months to 6 years. The etiologic factors given included enlarged tonsils and adenoids, sinusitis of other sinuses, rhinitis, otitis media, influenza, syphilis, measles, scarlet fever, malnutrition and foreign bodies

in the nose. The organisms most often encountered were the influenza bacillus, the pneumococcus, the streptococcus and the diphtheria bacillus.

The most constant symptom was a persistent nasal discharge. Other symptoms varied with the severity of the attack and the complications involved. Diagnosis was made by direct examination in some cases, by roentgen examination in others and by both methods when possible. Roentgen examination is of great value even in children; it is the only means of making a diagnosis in many cases. Complications consisted of various degrees of orbital involvement; in some cases even orbital abscess, meningitis, coexisting sinusitis in other sinuses, mastoiditis, otitis, arthritis and nephritis were found.

Treatment was conservative, aiming at simple drainage by shrinking the mucosae when possible, as with ephedrine. More radical means consisted of irrigation or operation. The latter method, however, should be attempted only after the operator has had a great deal of experience in this field, because of the grave danger involved. Ultraviolet irradiation seemed to help in most cases, and general hygiene was of especial value.

BARNETT, Chicago.

OTITIS MEDIA: ITS COMPLICATIONS, MANAGEMENT AND TREATMENT. J. THOMAS DOWLING, Northwest Med. **27**:472, 1928.

Of twenty cases of otitis media, Dowling found paranasal sinusitis in fifteen. Fourteen of these children were poorly nourished and were artificially fed. He believes that otitis is often secondary to sinusitis. He remarks on the frequency of bronchopneumonia, pyelitis and gastro-intestinal disturbances in association with the otitis. These may be secondary to, or they may be the cause of, the otitis. He believes that the streptococcus is the most frequent causative agent.

SCOTT, Philadelphia.

IMPORTANT PROGRESS IN THE ART OF INSTRUCTING DEAF MUTES; THE BELGIAN METHOD OF DEMUTATION. E. DROUOT, Rev. franç. de pediat. **4**:343, 1928.

The Belgian method of demutation consists in accepting the fact that children up to about 9 years of age have an appreciation of things as a whole and are rarely interested in or capable of analysis. Instead of being taught to talk by learning individual sounds and then putting these together to form words, they are made directly acquainted with objects or actions, the written symbols for them and the appearance of the lips in naming or describing them. This claims their interest and enthusiasm; they write easily and finally can say words and phrases through imitation, as the small child talks without the painful putting together of one sound after another. The advantages of such a method are: (1) the children can be taught much younger than when the method of analysis is used; (2) they thoroughly enjoy their learning and can acquire ideas at the same rate and time as other children, and (3) their speech is easier and more natural and rapid talk does not interfere with their ability to read the lips.

LESLIE, Evanston, Ill.

THE INDICATIONS FOR TONSILLECTOMY IN ARTHRITIS AND SO-CALLED RHEUMATIC DISEASES. JOSEPH SCHNEYER, Wien. Arch. f. inn. Med. **16**:119, 1928.

The author recommends tonsillectomy, regardless of the condition of the tonsils, in acute polyarthritis rheumatica after the acute stage of the disease has passed; he also recommends this operation for secondary chronic polyarthritis.

In rheumatoid disorders such as the myalgias and neuralgias, tonsillectomy is advised only if the tonsils actually give evidence of disease and some connection can be established between the disease and the myalgias or neuralgias.

Tonsillectomy is contraindicated in primary chronic polyarthritis. The same is true for osteo-arthritis deformans and gout.

SCHLUTZ, Minneapolis.

Diseases of the Skin

ERYTHEMA NODOSUM IN CHILDREN. JULIUS H. HESS and S. L. BERMAN, M. Clin. N. Amer. **12**:49 (July) 1928.

The intimate relationship between tuberculosis and erythema nodosum has been strongly upheld for years by European observers. By Americans it has been considered in most instances as one manifestation of infection by the streptococcus group of organisms. Three cases are reported in which the clinical and roentgenologic evidence and the tuberculin reactions pointed to tuberculosis as the underlying factor. One interesting group of three children from one family entered the hospital with tuberculosis, evidently of recent origin, with a history of exposure for two months to their grandmother who died of the disease; one of these children developed an extensive erythema nodosum on the arms and legs. Two cases are reported which were evidently related to rheumatic infection, and in which careful tests failed to reveal the presence of tuberculosis. Rosenow made bacteriologic studies in one of these cases and isolated a diplobacillus from an excised node and from the blood, and similar organisms from the tonsils. Inoculation of animals produced subcutaneous nodes pathologically similar to the one excised from the patient.

Erythema nodosum shows a pathologic condition which is not specific for tuberculosis. A cellular infiltration is present in the deeper layers of the corium and especially in the subcutaneous fat and is localized about the vessels and glands. This consists of round cells, some multinuclear granulation, tissue cells and polymorphonuclear leukocytes. Fibrinous exudates may occur in the subcutaneous fat; occasionally there are small hemorrhages. The endothelium of the small vessels is frequently swollen and shows large nuclei.

SMITH, Ogden, Utah.

THE ETIOLOGICAL RELATIONSHIP OF TONSILLAR FOCAL INFECTION TO ECZEMA IN CHILDREN. D. M. SIDLICK, M. J. & Rec. **128**:344 (Oct. 3) 1928.

It is entirely feasible for a chronic septic focal infection to cause a skin disease, and for the removal of the focus to be followed by the disappearance of the process. An example of this is lupus erythematosus. The author made a study of forty-two children between the ages of 1 and 12 years, who were suffering from eczema. He referred all cases to the chiefs of the throat clinics. Patients whose tonsils were diseased were advised to have the tonsils removed. All cases were followed up for four weeks after the operation had been performed. With every one of the forty-two children, improvement was followed by recrudescence of the skin disease within two weeks after the operation.

EPIDERMOLYSIS BULLOSA HEREDITARIA, WITH THREE ILLUSTRATIVE CASES. RAYMOND GREENE, Proc. Roy. Soc. Med. **21**:1728 (Aug.) 1928.

According to the author, epidermolysis bullosa hereditaria is a rare hereditary skin disease, characterized by extreme sensitiveness of the skin to the slightest trauma. The least conspicuous irritation, knock or pinch immediately gives rise to intense irritation followed by the appearance of a bulla. Two types have been distinguished by Luithlen. In the first are found blebs containing blood-stained serum which heal without scarring. In the second type, the blebs contain blood-stained serum and heal with much scarring and permanent pigmentation. The second type shows nail dystrophy. Neither one primarily affects the health. The pathologic changes are not well understood.

The author then describes in full three cases and gives the genealogy, which he works out in full for three generations.

WILLIAMSON, New Orleans.

HERPES ZOSTER AND VARICELLA. HANS ALTERTHUM, Monatschr. f. Kinderh. **40**:330, 1928.

In an institution in Berlin, during the last eight years there were thirty-six cases of herpes zoster, of which twenty-three occurred in conjunction with varicella. The number of cases of varicella with herpes zoster was relatively much higher in the institution than the number of cases of pure varicella. Zoster occurred seven times from medication with arsenic or bismuth; six of these patients also developed varicella. Varicella and zoster varicellosis do not always produce an immunity against each other.

The author concludes that for all practical purposes patients with herpes zoster should be isolated.

A CASE OF CUTIS LAXA. G. ROSSI, Riv. di clin. pediat. **26**:137, 1928.

Photographs and the clinical history of a patient with cutis laxa are given. The child died of progressive weakness and malnutrition; necropsy was not performed. The author gives a lengthy résumé of the literature on this subject and speculates on the possibility that the thyroid or hypophyseal dysfunction plays an etiologic rôle.

HIGGINS, Boston.

LEINER'S DERMATITIS. ANNA SZENTLELEKY-SZASZ, Monatschr. f. Kinderh. **40**:362, 1928.

The author states that the condition known as Leiner's dermatitis is due to a vagotonia and an extremely labile nervous system. She has tried giving an injection of 0.3 cc. pituglandol-Roche every two days until from five to six doses were given. Decided improvement seemed to result.

GERSTLEY, Chicago.

Surgery and Orthopedics

MULTIPLE SUBCUTANEOUS ABSCESSES. W. J. DONOVAN, Proc. Roy. Soc. Med. **21**:1320 (June) 1928.

The author reports a case of abscesses on the knee, abdomen and buttock of a child, aged 4 months. He aspirated the abscesses and obtained pus; the culture was sterile. The child was given irradiation.

WILLIAMSON, New Orleans.

THE DIAGNOSIS AND OPERATIVE TREATMENT OF SPLENOMEGALY. N. W. SCHWARTZ, Arch. f. klin. Chir. **149**:356, 1928.

Attention is called to the interest taken by both pathologists and clinicians in hyperplasias of the spleen. Splenectomy in certain conditions, such as Banti's disease, hemolytic icterus, essential thrombopenia and occasionally hypertrophic biliary cirrhosis, has been helpful. Some observers are of the opinion that any enlargement of the spleen is an indication for its surgical removal, but there is no question but that such a procedure is often useless, even fatal. The various forms of splenomegaly do not have, as yet, a sufficiently constant clinical picture, because their etiology and pathogenesis are still confused. Two cases of splenomegaly in which splenectomy was performed are reported to illustrate this contention.

In the first case, Banti's disease was present in a girl, aged 10 years. A severe hemorrhage occurred, and the spleen was removed. The patient was dismissed from the hospital in four weeks. The spleen weighed 595 Gm. Microscopically, its structure corresponded definitely to that in Banti's disease.

The second case of splenomegaly associated with splenectomy was one of hemolytic icterus. Microscopic sections did not reveal changes suggesting a hemolytic icterus, in spite of the fact that the spleen weighed 550 Gm. The outcome, however, was good.

In his summary, the author states that the microscopic changes occurring in various forms of splenomegaly may be identical but may give entirely different pictures clinically or may not have the characteristics of any known disease; because of this confusion, one cannot attach great significance to microscopic changes in clarifying the pathogenesis of certain forms of splenomegaly. Such a difficulty is frequently encountered in a differential diagnosis of Banti's disease, hemolytic jaundice and hypertrophic biliary cirrhosis. There are conditions of splenomegaly that seem to represent a mixed form of the foregoing three hepaticosplenic disturbances that have not been investigated from either a clinical or an etiologic and pathologic standpoint.

The author feels, however, that in spite of the frequent difficulty of diagnosis, splenectomy is at least a rational type of treatment, because of the successful results in the majority of cases. He warns that one must make certain that the splenomegaly is not based on a systemic disease such as a leukemia in which splenectomy is contraindicated.

Osteitis Fibrosa of the Jaw and Its Influence on Dentition. Karl Spring, Arch. f. klin. Chir. **149**:385, 1928.

The author discusses osteitis fibrosa of the jaw from a differential standpoint, mentioning especially sarcoma, acute osteomyelitis, cystic adamantinoma and syphilis. He reports a case in which these conditions could easily be confused. He also reviews the literature of osteitis fibrosa and evolves the following classification: (1) cases in which the lesion is in the region of the frontal, temporal or zygomatic bones; (2) those involving the maxilla or mandible and (3) those involving the temporal and maxillary bones.

The case reported belonged to the second group. There was a diffuse involvement of the entire mandible, leaving uninvolved only the articular surfaces and the coronoid process. Histologically, the tumor tissue consisted of many spindle-shaped cells with irregularly distributed connective tissue fibrillae. A considerable number of giant cells were formed which were uniform in size, with sharp borders; their nuclei were deeply and uniformly stained. Many cells lay in typical lacunae as osteoclasts, while on one side there was a definite row of osteoblasts. Blood pigment also was present.

The upper jaw did not reveal a change in respect to dentition. In the lower jaw, the condition was quite different. There was a disturbance of the alveolar processes, similar to that found in experimental animals: The teeth either failed to erupt, instead remaining embedded in bone, or they erupted in false places. In addition, there was destruction of the roots of the unerupted teeth and some of those already erupted. These changes were most marked in the region of the molars and premolars; the front teeth were relatively unchanged.

The Subperiostal Resection in Severe Rachitic Deformities, and the Subsequent Process of Bone Regeneration. H. Schloessmann, Beitr. z. klin. Chir. **143**:365, 1928.

Attention is called to the fact that von Schepelmann in 1918 was the first to undertake a subperiosteal resection of a rachitically deformed tibia and that after that time many methods were devised for the procedure.

Fundamentally, all methods fall into one of the two following groups: (1) The periosteal cavity is left empty or partially empty, or completely filled with blood, and (2) the periosteal cavity is partially or completely filled with bone substance, taken from a neighboring bone, the resected portion or a heterogenous source, for the purpose of furnishing building material for the regeneration of new bone.

During a period of five years nineteen rachitic children were operated on; since many of them had a bilateral operation, thirty-five resections in all were done. In eleven resections, the periosteal cavity was left empty; in eighteen, the author performed a resection with reimplantation of fragments of the resectioned

segment (a method developed by Springer), and in six, the whole shaft was replaced by a solid transplant. The interesting feature about this work was to observe the regeneration of bone by the three methods employed and to watch their behavior under identical conditions.

As a whole, the results were good. Such complications as infection, pseudo-arthrosis and "slowly sliding" fractures were encountered in a small percentage of instances. In fact, the advantages gained in the transplant method were not noteworthy, and all the methods used gave equally good results. The author advocates the simplest method, namely, subperiosteal resection with immobilization for from eight to twelve weeks. In addition, he uses the general measures of antirachitic treatment such as fresh air, sunshine, phosphorus and calcium, irradiated ergosterol and the ultraviolet ray.

Observation of new bone regeneration in roentgenograms disclosed small linear streaks appearing in from eight to ten days in the region in which resection was performed. By the end of eight or ten weeks, the formation of new bone is fairly well established. There is a noticeable decrease, however, in the calcium content of the bone in which resection is not done, at about the time that ossification begins in the excised areas. This process of decalcification is more marked and rapid and that of recalcification slower in the distal than in the proximal fragments. The marrow spaces in the regenerated areas are noticed in from nine to ten months after the resection. At about this same time the marrow cavity is restored. In the author's opinion, the new bone regenerates from the periosteum. The roentgenograms of his material did not substantiate the prevailing opinion that marrow and cortical bone also participate in the new bone-forming process.

OBERHELMAN, Chicago.

Miscellaneous

AN APPARATUS FOR METABOLIC EXAMINATIONS IN INFANTS. A. BRATUSCH-MARRAIN, Arch. f. Kinderh. **85**:8 (Aug. 31) 1928.

The apparatus consists of a waterproof ring and pad on which the infant is placed covered by a waterproof band. This is fully illustrated by photographs accompanying the article. The apparatus has been used successfully in several cases of erosive dermatitis caused by acid stools and of gastro-intestinal derangements. The excreta are easily collected, and the child's buttocks are not irritated.

STUDY OF THE PHYSICAL STATUS OF THE URBAN NEGRO CHILD. E. BLANCHE STERLING, Pub. Health Rep. **43**:2713 (Oct. 19) 1928.

An intensive study of a group of more than 5,000 negro school children from 6 to 14 years of age, in Atlanta, Georgia, has brought out many interesting facts. Girls exceed boys of the same age in height much earlier among negro than among white children; further, in negro children this advantage is maintained longer. In weight, negro girls tend to become heavier than negro boys at a slightly earlier age than that at which white girls outweigh white boys; the superiority in weight of negro girls is decidedly greater than that of white girls and continues until the age of 14. In breadth and depth of the chest, the relationship of the sexes is also different in the two races. In breadth and depth of the chest, the negro boy has a slight advantage over the white boy. The heads of negro children are more of the long type than are those of white children. The convex type of scapula was the most prevalent among the negro children, while among the white children there was a district preponderance of the scaphoid type. Excellent teeth were found in 64 per cent of the negro children. The incidence of skin disease and heart defects was low. In 12.69 per cent of the children, two evidences of rickets were found in the bony structure; single changes were noted in a large percentage. The apparent mildness of deformity from rickets, however, was striking.

SANFORD, Chicago.

IMPORTANCE OF THE DAY NURSERY IN RELATION TO THE CHILD WELFARE MOVEMENT. Rev. internat. de l'enf. **6**:584, 1928.

There exists in all industrial countries, and possibly to a lesser extent in others, a class of mother and child that is apt to be passed over by the child welfare institutions.

This class consists of the mothers who are obliged to work and the children who are consequently neglected. Social workers cannot reach these mothers because they are never at home when welfare organizations are functioning. A widow's pension in England, for example, is not sufficient to support her and her children; she must work. Again, many women are deserted by their husbands and are forced to work, or starve. There is also always the problem of the unmarried woman with children. Certain industries are entirely dependent on women's labor, and certain forms of service, such as those provided by charwomen and office cleaners, are universally offered to female employees. When the father is ill of chronic disease, the mother must enter the lists of competitive labor. In all of these instances children of preschool age suffer from inattention and neglect; there is no one to accompany them to a welfare center and they are indifferently looked after by a neighbor, when not farmed out to some ignorant old woman. Frequently little ones of 2 or 3 years of age must be left alone to fend for themselves the entire day.

There is only one outstanding measure of relief for these unfortunate children — the day nursery, or crèche. Here they are properly fed and cared for and the mother learns the rudiments of child hygiene and home making. The Viscountess Erleigh sponsers a movement to incorporate these life saving stations as an integral part of all welfare programs. She believes that the reason this obviously supreme agent in the saving of child life has not received the attention it deserves is an economic one. The cost of maintenance is indeed excessive when only small units are cared for, but it has been demonstrated, as in the Deptford Nursery and the Sun Babies Day Nursery, London, that groups of more than 300 children of from 2 to 5 years of age can be supervised, and the older ones educated, at a modest expense.

AMESSE, Denver.

THE HEALTH CONDITIONS OF THE CHILDREN OF FRANKFORT-ON-THE-MAIN. HAGEN, München. med. Wchnschr. **75**:1450, 1928.

Approximately 35,000 school children and 6,000 children of preschool age were examined. The methods of evalution and classification differ somewhat from those followed in this country. The children are divided into four groups: (1) well children without defects; (2) those below par but without disease; (3) those below par but with disease, and (4) strong children with single defect.

Reference is made to the observations, as figures for comparison may be sought by American pediatricians.

SCHORER, Kansas City, Mo.

THE MORTALITY RATE OF ILLEGITIMATE INFANTS. S. LEVY, Ztschr. f. Kinderh. **45**:675 (June) 1928.

Levy is convinced that the span between the mortality rate of legitimate and illegitimate infants can be narrowed if illegitimate children, after staying with their mothers as long as possible, are kept in an institution for the first six months and then placed in private homes.

EMERSON, Boston.

DIAGNOSIS FOR CHILDREN DELIVERED BY FORCEPS; A REINVESTIGATION OF TWO THOUSAND CHILDREN DELIVERED BY FORCEPS AND TWO THOUSAND SPONTANEOUSLY DELIVERED. WETTERDAL, Acta obst. et gynec. Scandinav. **6**:349, 1927.

The author followed the record of 4,000 children who were born between the years 1900 and 1914. Of these, 2,000 were delivered spontaneously and 2,000 by forceps. Seven hundred and fifty-six of the children died before the age of 12.

and 2,770 were found alive at this age, making a total of 3,526, or 88.15 per cent, available for investigation. Of the 2,000 infants delivered spontaneously, 2.55 per cent died in the hospital, 15.7 per cent died after discharge and 11.7 per cent could not be traced. At 12 years of age, 72.5 per cent of the children were in good health; 6.6 per cent were mentally defective, and 5.3 per cent were physically defective. The cases in which forceps were used are divided into the following groups, according to the operative indications:

1. Of 1,049 infants delivered with weak pains and the head on the pelvic floor, 3.6 per cent died in the hospital; 16.2 per cent died after discharge; 13 per cent were not traced; 72.5 per cent were in good health; 6.7 per cent were mentally defective, and 4.5 per cent were physically defective.

2. Of 146 infants delivered with weak pains and the head not on the pelvic floor, 6.2 per cent died in the hospital; 12.4 per cent died after discharge; 71.7 per cent were in good health; 9.9 per cent were mentally defective; 6.2 per cent were physically defective, and 17.5 per cent were not traced.

Five hundred and thirty-six delivered by forceps had asphyxia neonatorum. Of these infants, 16.8 per cent died in the hospital; 15.9 per cent died after discharge; 74.5 per cent remained in good health; 5.6 per cent were mentally defective; 4 per cent were physically defective, and 15.5 per cent were not traced. One hundred and nineteen infants delivered by forceps had eclampsia; 21 per cent of these died in the hospital; 18.8 per cent died after discharge; 72.9 per cent remained in good health; 5.9 per cent were mentally and 2.5 per cent physically defective and 9.6 per cent were not traced. Of 150 infants delivered by forceps because of various maternal diseases, 16 per cent died in the hospital; 14.2 per cent died after discharge; 77.9 per cent remained in good health; 7.96 per cent were mentally defective, and 10.3 per cent were not traced.

While the primary mortality is higher among infants delivered by forceps than among those delivered spontaneously, the remote results seem to be equally good, especially for those delivered by low forceps. The main factors influencing the results for the infant are: (1) its development at birth; (2) the parity of the mother and (3) the time elapsing between the rupture of the membranes and birth. The author concludes that the poorer primary results in delivery by forceps are largely due to the fact that many of these deliveries are more difficult and present other factors than the use of forceps.

The author summarizes his investigations as follows: "Deliveries by forceps are burdened with a primary mortality for the children varying for the different indications for which the forceps are applied: further, in cases of low forceps operations, excluding those for asphyxia in the fetus, the primary mortality exceeds very slightly (about 1 per cent) that associated with spontaneous deliveries. As the results are the same, whether the head has engaged on the pelvic floor for two or more hours, an early application of forceps is recommended in cases where labor has ceased. Some cases of asphyxia can thereby be avoided, the results for all children being consequently improved. In all categories of those delivered by forceps on different indications the results are reflected on the primary mortality. When compared with those spontaneously delivered no inferiority can be detected in those delivered by forceps so far as the mental and physical conditions at the age of 12 are concerned. As exceptions from the above conclusions we have the intermediate and high forceps operations, when these are dealt with separately, independently of the forceps indications. For these forceps applications, employed as a rule on some absolute indication from the standpoint of mother or fetus, have been shown to be associated with very much more risk for the child by way of serious mental defects than is the case with those spontaneously delivered or with children delivered by low forceps."

ADAIR.

Society Transactions

AMERICAN CHILD HEALTH ASSOCIATION

Chicago, Oct. 15-19, 1928

Pediatrics Service in City Health Department Centers Provided by Medical Schools in Boston. Dr. Harold C. Stuart.

The well infant and preschool child health conferences of Boston are conducted by the Division of Child Hygiene of the city health department. They are held in municipal health centers, and the nurses in attendance are in the employ of the city; the physicians are appointed and supervised by the three medical schools of Boston. It was felt that the usefulness of free health conferences in the prevention of disease, by providing frequent examinations of well infants and preschool children, by giving mothers instruction in feeding and hygiene and by securing an earlier and more general immunization of the community against communicable diseases, had been amply demonstrated.

It is essential that the physician of the future shall be not only more adequately informed about, but shall be more interested in, preventive medicine. So long as the student's entire clinical experience is obtained at the bedside of acutely or chronically ill persons, his knowledge of the problems of preventive medicine and hygiene will be difficult; without experience or knowledge, his interest will inevitably fail. Many physicians who claim to be specially trained in the diseases of infancy and childhood have an inadequate knowledge of the well infant and child, and many general practitioners have no conception of the nature of these problems or how to handle them.

Attention was called to the need for better instruction of medical students and interns in problems of child hygiene and preventive medicine.

DISCUSSION

Dr. William H. Peters, Cincinnati: I hesitate to discuss the classic presentation of Boston's pediatric service, by Dr. Stuart. So little remains to be desired, as I review the address.

Dr. Wilinsky has set a good example for the country at large, and his skilful leadership may serve to pave the way for health departments in many cities. No one, I dare say, will question a city's responsibility to provide preventive health service for preschool children. The city of Boston and the Community Health Association are both to be congratulated; the former for accepting its responsibility, the latter for its fine cooperation.

The purpose and policy of the well infant and preschool child health conferences of Boston are sound. They are not unlike those of many other cities where splendid progress has been made. The manner in which the clinicians confine themselves strictly to educational prophylaxis is something of which we should all take cognizance.

Perhaps the time will come when it will no longer be necessary to provide such examinations as are given at these conferences free of charge to those who are well able to pay for medical service.

I am not alarmed about the relationship, or shall I say opposition, of the medical profession to health conferences. The antagonism which creeps into medical journals occasionally is grossly exaggerated. The real difficulty is that the family physician has not been trained in preventive pediatrics. What Dr. Stuart is doing in training medical students, the very thing that is being done in Cincinnati, is fundamental. When the family physician is capable and willing to do the kind of work which is being done in the preventive clinics, there will be no antagonism. Difficulties will disappear to the vanishing point, as long as the treatment is limited to underprivileged children.

At the present time in every large city where child health conferences are under way, thousands of mothers seek the advice of their own physicians. The clinics, therefore, have a tendency to stimulate private practice rather than retard it.

Perhaps the outstanding thing in Dr. Stuart's paper is the cooperation of the medical schools in Boston under the arrangements which have been described. Obviously, this arrangement is not only a great boon for the health conference, but it also is of inestimable value to the undergraduates in the study of child hygiene.

While the Boston plan is better from an administrative standpoint, it may not be amiss to state briefly what is being done in Cincinnati. The Health Department plays a minor rôle. The builk of the work, as it relates to baby clinics and preschool child conferences, is carried on by the Babies' Milk Fund Association with an annual grant of approximately $60,000 from the Community Chest. The organization, as the name would indicate, is not a milk distributing agency. It distributes milk solely to underfed and undernourished children whose parents are too poor to provide a sufficient amount of milk.

Six child health stations are supported which, under a full-time physician, twelve part-time physicians and a complement of twenty nurses, supervise the health of children under 6 years of age, and direct the mothers in the care and feeding of well infants under 1 year of age. Five of the stations are scattered throughout the poorest section of the city. The principal station, operated daily, is located at the Cincinnati General Hospital. All other stations, with one exception, hold conferences twice a week. These stations cater to a clinic class of patients. About 35 per cent of the children are subject to treatment. A social service worker determines whether children are entitled to free dispensary service or should be referred to private physicians.

All the health station physicians are members of the pediatric department of the College of Medicine, University of Cincinnati. They are paid at the rate of $2 a session.

All children dismissed from the pediatric department of the General Hospital are discharged through the Babies' Milk Fund Association, and immediately become observation cases of the outlying health stations.

One station, with a registration of 400 infants last year, specializes in the prevention of rickets by ultraviolet-light treatments.

An excellent brace shop is maintained by the Babies' Milk Fund Association. Braces are furnished free of charge, or at a nominal cost depending on the patient's ability to pay.

The Babies' Milk Fund Association is also responsible for the health supervision of the infants and young children in eight day nurseries. Every nursery, not unlike every health station, is also a teaching center for medical students. The knowledge gained is applied in home visiting. This is a regular accredited part of their course in pediatrics. All children are immunized against diphtheria.

For fifteen years or more the Babies' Milk Fund Association has been functioning effectively in the field of Preventive Pediatrics. The city should assume this burden, and thus permit the Association to function along other lines.

One of the most significant pieces of child health work in Cincinnati is the home contact which the public health nurses of the Health Department make following the report of a birth, under an arrangement which is almost identical with that of the Boston City Health Department. The nurse leaves a copy of the birth certificate which has been properly recorded together with suitable literature, and urges the mother to place the infant under medical supervision. Thus, she has an opportunity to advise mothers, especially those who have been unfortunate, to seek proper care before the next baby is born.

The Department of Health conducts a well baby clinic and preschool child conferences at the Health Center which houses a diagnostic chest clinic, an adult dental department, a heart clinic, a clinic for the control of venereal diseases, a children's department and the administrative offices of the public health nurses.

During the summer months, well baby and preschool child conferences are conducted weekly by the Health Department in the poorer sections of the city. This temporary makeshift is valuable in stimulating a more widespread interest

in preventive pediatrics. When the stations close the cases are referred to the health stations of the Babies' Milk Fund Association.

One of the best pieces of work is the Summer Round-Up of Preschool children, which is an annual event, sponsored by the Health Department, the Parent-Teacher Association, and the Public Health Federation. Twenty-four hundred children in seventy-eight schools were examined this year. This represents about one fourth of the first grade enrollment. The Parent-Teacher Associations undertook the registration of the children.

In the examinations, scheduled by appointment, the district physicians were assisted by the public health nurses and a group of dentists who volunteered their services. Making children free to gain in health and mental vigor was a delightful occupation of the nurses during the summer months. It is pleasing to tell you that before the follow-up began 50 per cent of the children were under the care of their family physicians. In this movement we had the cooperation of all hospitals and clinics.

PRESCHOOL HEALTH SUPERVISION IN SMALL TOWNS AND RURAL AREAS. DR. ELIZABETH M. GARDINER.

With the reorganization of the Child Hygiene Division of the New York State Department of Health which took place in 1922, it was recognized that to be effectual supervision of the preschool child must be more or less continuous and routine, and that the realization of this ideal could be looked for only where child hygiene was carried on as an integral and permanent part of the local public health program.

To date, the supervision of preschool children in New York State has been exercised through the following activities and services:

1. The state department of health conducted child health consultations and examined children from 6 months to 6 years of age.

2. Staff members were placed as demonstration child hygiene nurses in counties or rural areas; a full maternity, infancy and preschool program was developed, and the demonstrations were conducted in such manner as to convince the public of the need of the work.

3. Allotments of the Federal funds to the extent of $800 per annum in each case to assist in securing public health nurses were made available to ten counties and twenty municipalities of 5,000 population or under with high maternal and child death rates.

4. Financial assistance in the form of annual allotments for the payment of local physicians, who worked with local departments of health for the examination of infants and preschool children, was afforded to many local municipalities of sufficient population to justify the holding of clinics once a month.

5. Specialized staff assistance was given to local independent nursing organizations, for the formation and carrying on of mother and child health stations.

6. Financial assistance was granted to local counties for the payment of groups of physicians appointed by and working under the auspices of the county medical societies in conjunction with local health officers, for the purpose of examining preschool children twice yearly in the sparsely populated rural areas.

There is still too low a percentage of corrections with very little available in the way of organized assistance for the cases in which there are no financial resources for the necessary corrective work. This is particularly true where there are no hospitals. This is the next task before us.

A REVIEW OF SCHOOL HEALTH WORK. DR. JAMES FREDERICK ROGERS.

For a comprehensive view of the field of endeavor in school health work, Dr. Rogers says that we must realize that notwithstanding the difficulties to be overcome, the unscalable heights of heredity, the inertia of school officials, the ignorance and prejudice of parents, the limitations of knowledge regarding communicable disease and nutrition, an excellent progress has been made. The odds

are still heavy, but the discontent with what we accomplish, which brings us together at this time, is indicative of more effective plans for future campaigns.

We do not have to count from the days of Mulcaster and Cogan to discover progress. Only fifty years ago, that vigorous apostle of public health, the Reverend Charles Kingsley, wrote "The teaching of health ought to, and will, in some more civilized age and country be held a necessary element in the school course of the child; just as necessary as reading, writing or arithmetic, for it is, after all, the most necessary of that technical education of which we hear so much, namely, the technic or art of keeping alive and well." Evidently, we belong to that more civilized age and we can rejoice that Kingsley's prophecy has been fulfilled to such a degree, although there still remains so much to be accomplished.

FIVE YEARS OF HEALTH WORK FOR PRESCHOOL CHILDREN IN THE GENERAL PROGRAM OF THE EAST HARLEM NURSING AND HEALTH DEMONSTRATION. MABELLE S. WELSH, R.N.

During the past five years, the East Harlem Nursing and Health Service contracted for health supervision and sickness care of 4,464 children between the ages of 2 and 6 years. In the same period, similar services were rendered 3,225 infants, 25 per cent of whom, or 380 infants, were transferred to the preschool service. The preschool service received 18 per cent of its enrollment directly from the infant group with no break in the continuity of services. With 313, or 5 per cent of the group, the first contact was made through personal illness. The majority of first contacts, 77 per cent, were made through the morbidity, maternity, infant and other services of the general health program.

The nursing and health service operated in a single restricted area in New York City. The population unit served was approximately 40,000, with an estimated annual average of 4,368 preschool children. The service reached approximately one fifth of the preschool population.

The most common physical defects noted by the medical examiners were poor posture, carious teeth, malnutrition and diseased tonsils. In these four groups fall 94 per cent of all defects noted, exclusive of those that are temporary and others that are uncorrectable. In the infant group, one finds that rickets, malnutrition, hypertrophied tonsils and adenoids account for 71 per cent of all diagnosed defective conditions.

Seventy-one per cent of 1,752 children examined in the medical conference were given Schick tests; 57 per cent of the children gave negative reactions and 43 per cent reacted positively and were immunized against diphtheria. Forty-nine per cent of the positive reactions were found in children 2 and 3 years old and 36 per cent in children aged 4 and 5 years. The practice of making Schick tests was abolished in 1927, except for children who had previously been given toxin-antitoxin in infancy. There were eleven cases of diphtheria with one death among the preschool children.

There were 597 cases of nursed illness in the group of 4,464 children during the period of supervision, which averaged approximately eighteen months per child. During the same time, forty-one deaths occurred, twenty-five of which were in the group of nursed cases and sixteen in the general group. The forty-one deaths include all deaths in hospitals. An analysis of the cause of death in the sixteen nonreported cases showed that four deaths were due to accident and one to a sudden convulsive seizure; three children had been sent to hospitals. Eleven of the children had been visited within the month when death occurred, and six had been visited within ten days.

During a five year period of this intensive health service, approximately one fifth of all the preschool children, in the community were reached in a joint program of health supervision and care for sickness.

The continuity of health services was maintained by means of the general character of the health program. The policies of the preschool service were established through knowledge gained in home visiting for other services. Work for preschool children was closely correlated with infant care. Sick children were not transferred to another agency for bedside nursing service.

The problems of the preschool years, physical and emotional, have their origin in the home and must be attacked at the source to prevent serious difficulties in later years. Work for preschool children should begin with or before the birth of the child and be continued until all parents are sufficiently intelligent to recognize deviations from a desirable standard of health and are in a position to get the help they need for their children as soon as that need is present.

PRESCHOOL HEALTH SUPERVISION IN A LARGE CITY BY A VOLUNTARY AGENCY. DR. EDGAR J. HUENEKENS.

The Minneapolis Infant Welfare Society was organized in 1910; a special department for preschool children was inaugurated ten years later. As a result of the experience gained, habit training has been extended to the infant clinics, and the upper age of infants has been extended to 4 years. In the preschool clinics, 70 per cent of the children are referred from the infant department, and the remainder come from clinic mothers. In order to obtain a cross-section of the work, 400 cases were analyzed. It was found that most children were taken to the clinic for general advice; the next common reasons were feeding and loss of weight. The clinic found that the majority of these troubles were due to lack of understanding by the parents and to the home environment. The number of children actually having physical defects was small. It may be concluded that before the age of 6 years the character and the emotional patterns have been formed for life. If this is true, the best time for a mental hygiene program is during the preschool years, and a preschool clinic should consider the emotional side of a child's life equally if not more important than the physical side.

ST. LOUIS PEDIATRIC SOCIETY

RALPH L. COOK, M.D., *Secretary*

Oct. 12, 1928

J. PARK WHITE, M.D., *Chairman*

A CASE OF EPENDYMITIS. DR. GEORGE H. GARRISON.

A girl, aged 6 years, entered the hospital with a complaint of headache, stiff neck and vomiting of forty-eight hours' duration, and of sore throat and generalized convulsions of thirty-six hours' duration.

Examination revealed an apparently rational child; the neck was freely movable. The Kernig and Brudzinski signs were negative. The tonsils were enlarged and reddened, and the anterior cervical glands were enlarged. The temperature was 102 F.; otherwise, the child was normal.

Thirty-six hours later the patient became drowsy and developed left internal strabismus. Lumbar puncture revealed clear spinal fluid under increased pressure and a cell count of 35, of which 48 per cent were lymphocytes. The patient gradually developed some stiffness of the neck, a positive Brudzinski sign and inequality of the pupils. She became stuporous, occasionally crying out as if in pain. The temperature was normal. Defecation and urination were involuntary. Results of x-ray pictures of the chest and skull, the Pirquet and Wassermann tests, culture of the spinal fluid and guinea-pig inoculation were negative. Lumbar puncture repeated at intervals of from two to four days, as symptoms indicated, always showed an increase in pressure and a cell count of from 35 to 50.

The condition remained unchanged until six weeks after admission, when the patient spoke a few words with difficulty. Within the next two weeks she showed marked improvement in speech, took an interest in her surroundings and began to feed herself. Eleven weeks after admission the patient was discharged; there was some spasticity and limitation of the motion of the right arm and the right

leg. At the present time, four and a half months since the onset of the illness, the patient is apparently well, and without residual observations. The condition was diagnosed as ependymitis.

PNEUMOCOCCIC PERITONITIS. DR. GEORGE H. GARRISON.

A girl, aged 3, was sent to the hospital with abdominal pain, diarrhea, fever and vomiting of forty-eight hours' duration. Typhoid fever was suspected. Examination showed the legs flexed and abdominal tenderness, most marked in the right lower quadrant. The white cell count was 11,400; results of the Widal test, examination of the urine and the stools and cultures of the blood were negative. The surgeon thought that the condition of the abdomen would not require surgical intervention. The temperature remained from 101.5 to 103 F. throughout four days. On the fourth and fifth day, râles were heard in the chest. The patient vomited on the fifth and sixth days in the hospital. The white cell count rose to 10,800; the abdomen was distended. On laparotomy a thin yellowish pus without discernible odor escaped from the abdomen.

A limited postmortem examination showed a purulent exudate over the lower 6 inches (15.2 cm.) of the ileum. No perforation was found, and the appendix was apparently normal. Section of the intestine on microscopic examination failed to show any evidence of a typhoid lesion. Culture of the fluid of the abdomen at the time of operation showed a gram-positive *Diplococcus,* which was not further identified.

A CASE OF ACUTE HEMORRHAGIC NEPHRITIS AND LOBAR PNEUMONIA WITH SIMULTANEOUS ONSET. DR. KATHERINE BAIN.

A boy, aged 12, whose past history was negative, suddenly developed headache, fever, vomiting and abdominal pain. The vomiting and extreme abdominal tenderness suggested appendicitis; twenty-four hours later, however, the clinical picture was that of pneumonia without definite signs in the chest. The urine at this time contained gross blood, albumin and many casts and leukocytes. The course was typical of lobar pneumonia, the crisis occurring on the seventh day. The lung signs, which did not appear until the day preceding the crisis, were in the upper lobe of the right lung. Following the crisis the urine cleared rapidly, and the patient made an uneventful recovery.

A review of 175 cases of acute hemorrhagic nephritis, occurring in the Saint Louis Children's Hospital between 1915 and 1928, reveals the fact that in eight, or 4.6 per cent, the conditions followed an attack of primary pneumonia. These cases were similar to the one already recorded. A brief review of the literature discloses few references to nephritis as a complication of lobar pneumonia. Nobécourt reported several cases and believes the nephritis to be due to the pneumococcus. This seems illogical since the streptococcus is known to be the cause of the majority of cases of hemorrhagic nephritis, and since the streptococcus may be associated with pneumonia, either as the causative organism or as a secondary invader.

A CASE OF OVARIAN CYST WITH ACUTE APPENDICITIS IN A CHILD 15 MONTHS OF AGE. DR. FRANZ ARZT.

A child, aged 15 months, was presented because of fever, constipation and vomiting on two occasions over a period of twelve hours. The child suddenly cried out with pain on moving or on being moved, and refused food and water. Vomiting was not projectile. The temperature was 100 F. (axillary), and on examination there was tenderness and some muscle spasm in the right lower quadrant. No mass was made out. The child's mother was instructed to give only water by mouth and warned not to give any cathartics. An enema was given which returned clear. Twelve hours later there was no further vomiting, the temperature increased to 101 F. and the pulse was extremely rapid. On examination there was marked rigidity in the right lower quadrant and extreme tenderness on palpation of the abdomen. The child was then taken to the hospital, and

four hours later was examined by Dr. Park White. The temperature then was 102 F. (rectal). The white blood count was 13,600; a catheterized specimen of urine was negative. Examination of the ears, throat and chest did not reveal any abnormalities. The abdominal examination was as previously described except that Dr. White made out a mass in the right, lower quadrant, and the abdomen was now moderately distended. It was believed that this was a case of acute appendicitis, that the appendix had ruptured and that the mass apparently was an abscess. An immediate operation was advised.

With the patient under ether anesthesia a right rectus incision was made. On opening the peritoneal cavity the appendix came into view; it was enlarged, injected but unruptured. A relatively easy appendectomy was done, and the stump inverted with a purse-string suture. Exploration of the abdomen then revealed a large, cystic mass to the right of the pelvis. The tumor was freely movable on a rather small pedicle which was attached just to the right of a very small uterus. The abdominal incision was enlarged, and the tumor was delivered intact. The pedicle was clamped and cut and then ligated twice with 2 twenty day catgut. A small rubber dam drain was inserted into the right iliac fossa, and the abdomen closed in layers. The drain was removed on the third day. The child had an uneventful postoperative course and was discharged on the fourteenth day, the wound being completely healed at the time.

The pathologic diagnosis made by Dr. Richard Paddock was cystoma of the ovary and acute appendicitis.

Recurrent Unilateral Purulent Parotitis in Children. Dr. T. Wistar White.

Five children, from 4 to 8 years of age, had a unilateral parotitis. Purulent saliva was expressed from Steno's duct. In three cases the condition recurred from three to six times. While the condition in the other two has not as yet recurred, the cases are so similar in all other respects that they are included in this report.

In one of the children the swelling accompanied an acute sore throat; in another it followed the grip and recurs whenever the patient has a cold. The condition in the other three cases was apparently independent of any predisposing cause as have been the recurrences.

The size of the swollen gland, the fever and discomfort were in accordance with those symptoms usually seen in mumps occurring at this age.

The swelling lasted from four to about fourteen days. The cloudy saliva disappeared before the swelling.

A moderate leukocytosis was the rule; the highest being 16,000. Roentgen examination in two of the cases did not show any calculus.

Cultures contained streptococcus, alone in one and with other organisms in three; once a streptothrix was obtained.

Hot or cold packs were applied. Pilocarpine was given. In one, autogenous vaccine was given after the first attack, and the condition did not recur; however, it has recurred after each of two series of autogenous vaccine in another, and after one series in a third patient.

Two Cases of Rheumatic Carditis Treated with the Small Vaccine. Dr. John Zahorsky.

Two girls, aged 6 and 10 years, were suffering from rheumatism, endocarditis and pericarditis. Both showed the presence of numerous rheumatic nodules over the distal joints of the extremities. The latter also had marked choreic symptoms. After an ineffective attempt to influence the disease with salicylates, the Small vaccine (1:1100) was given hypodermically in doses beginning with 2 minims, and gradually increased. The injections were given every four to seven days.

The second patient proved exceedingly susceptible to the toxic influence of the vaccine, and only four injections were given. In the first patient, the rheumatic symptoms improved, the nodules disappeared, and the patient promptly recovered. The second patient suffered a relapse and died suddenly.

PINK DISEASE TREATED WITH YEAST. DR. JOHN ZAHORSKY.

This case occurred in an infant, 9 months old. The general symptoms were typical of Swift's disease. After six weeks of ineffective treatment with quartz light and tonics, the addition of yeast to the diet rapidly produced a change for the better.

ENTERITIS TREATED BY DYSENTERY VACCINE. DR. JOHN ZAHORSKY.

During the summer of 1927, twenty-four infants suffering from infectious enteritis, characterized clinically by fever and diarrhea with the passage of mucopurulent stools, were treated by hypodermatic injections of dysentery vaccine made from Shiga and Flexner bacilli.

The injections were given every three to five days. No death and not a single case of intoxication occurred. The impression was that the disease was made safer, and that it was somewhat shortened by these injections.

A CASE OF PELLAGRA. DR. JOHN ZAHORSKY.

The patient, a girl, aged 13 years, lived in the country and had been plump and well nourished until one year before the present illness. Having been teased about being too fat, she began to starve herself, soon lost her appetitite and subsisted on biscuits and jelly almost exclusively. She became very thin and lost 25 pounds (11.3 Kg.) in weight.

On clinical and laboratory examination nothing abnormal was found, with the exception of extreme emaciation, pigmented areas on the hands and back, and some erythematous scaly patches on the feet and arms.

A CASE OF CHRONIC MULTIPLE TENOSYNOVITIS. DR. T. S. ZAHORSKY.

A boy, aged 3 years, developed bronchopneumonia, following which he had an irregular fever, difficult breathing at times and swellings around the wrists and ankles. When seen in August, 1928, six months after the onset of the illness, there were tense, tender swellings of the dorsum of the wrists and ankles not in the points. The heart was enlarged; there were no murmurs; the lungs were clear. The nose and throat were free from infection. The joints were freely movable without pain. The blood showed moderate anemia, and leukocytosis. A blood culture did not reveal any growth. The urine was normal. Results of tuberculin tests were negative.

Salicylates were administered and he received several injections of vaccines, both mixed and also Small's vaccine. Aspiration of one wrist was performed, but only a small amount of yellowish mucinous material was obtained. Culture and smears remained negative. The irregular fever continued, some days as high as 104 F., and there was some reduction in tenderness and tension of the swollen tendon sheaths. At the present time he has gained a little in weight, and his appetite has improved.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Regular Meeting, Nov. 8, 1928

STAFFORD MCLEAN, M.D., *in the Chair*

THE RESULTS OF FEEDING OR INJECTING THE B. C. G. VACCINE IN ANIMALS DR. WILLIAM H. PARK.

The reports of those who have fed Calmette cultures to young animals are that no tuberculosis developed. On the other hand, those who have given from 5 to 50 mg. of the B. C. G. vaccine to animals subcutaneously have generally found an early development of tuberculous lesions, of slight extent. As a rule, these have disappeared in six months or more.

An interesting piece of work by Petroff showed that when Calmette's culture was planted on special mediums, two types of colonies developed, one being rougher than the other. These he called rough and smooth types. He found the culture from the smooth colonies to be moderately virulent, that from the rough colonies avirulent. When transferred to fresh mediums, the smooth colonies continued to produce largely smooth colonies. In his opinion, this development of a virulent strain from the Calmette culture on special mediums suggested a possible danger that a portion of the bacilli might become virulent in the body. Even if this did not take place immediately, he thought it might in later years. While Petroff's discovery is of great interest to bacteriologists, it does not suggest to me danger to those who receive the vaccine.

It is known that fully virulent bacilli are dangerous only in infants and very young children. They produce localized tuberculosis in older children, and practically no lesions in adults. There is, therefore, no reason to fear that attenuated bovine bacilli should become more virulent as the years pass. I feel, therefore, that his observations have little practical bearing on the use of the B. C. G. vaccine in infants. I believe that the fact that the bacilli have slight virulence gives more hope of their producing immunity.

My observations on animals fed and injected with B. C. G. vaccine have been of two kinds. First, there were the animals fed or injected at the Research Laboratories or at the Otisville branch. A number of monkeys, rabbits and guinea-pigs were subjected to subcutaneous vaccination, and guinea-pigs to oral vaccination. None of the animals which received the vaccine by mouth developed any lesions. In the animals which received the vaccine subcutaneously, a slight tuberculosis developed in some of them. This was confined largely to the adjacent lymph nodes, but in some there was a slight tuberculosis of the spleen and liver. So far as the development of immunity was concerned, I was not able to note any appreciable difference between the guinea-pigs fed large doses of vaccine at birth and those which had not received any vaccine. On the other hand, the animals which received subcutaneous injections showed a definite amount of immunity. When these animals were injected with human or bovine bacilli, they showed a much less progressive tuberculosis than those which had not received injections. So far then as the results with animals are concerned, there is no definite evidence that the oral administration of the vaccine was successful. It must be taken into consideration, however, that the epithelial lining of the intestines of the infant is different from that of animals. Also, natural infection is probably less severe than subcutaneous inoculations. My results would indicate that subcutaneous inoculations would probably be more effective than oral vaccination. The other observations were made by me in connection with Dr. King at the Sanatorium at Mount McGregor of the Metropolitan Life Insurance Company. Dr. King has recently reported his results at the meeting of the American Public Health Association. My portion in the experiment was as an observer and consultant. He utilized monkeys, calves and guinea-pigs. The general results with his larger group of animals were the same as I had had with my smaller group. An interesting case was that of a calf which, after subcutaneous inoculations with B. C. G., developed a positive tuberculin test. Later, the reaction became less marked and finally disappeared. After a year, the calf was put into a herd in which there were open cases of tuberculosis. The calf finally developed a positive tuberculin reaction and, when killed, showed fairly well marked lesions of tuberculosis. The experience with this calf corroborates Calmette's observations that immunity would not last much more than a year. The appearance of the first tuberculin reaction with its later disappearance suggests that immunity developed and disappeared with the reaction.

In Dr. King's tests, in one experiment, a guinea-pig developed progressive tuberculosis which, together with pneumonia, caused death. Whether this guinea-pig could have become infected with another strain of tubercle bacilli is impossible to affirm or deny. There is no evidence of any such possibility of infection. It can be said, therefore, that with this exception the experiments on animals indicate

that the vaccine is harmless but that as far as the taking of the vaccine by mouth is concerned, there is no definite proof that sufficient bacilli are absorbed to give a definite immunity to animals against a subcutaneous injection.

B. C. G. Vaccination in New York City. Dr. Camille Kereszturi.

Vaccination with the B. C. G. culture by oral administration was started in New York City in December, 1926. One hundred and thirty-three infants have been vaccinated, of whom thirty-three are over 1 year of age, the oldest being 20 months.

The tuberculosis situation is different here from in Europe, because the foci of infection are not so widespread, the social conditions are better and the general intelligence is higher. Consequently, I did not expect that the 25 per cent mortality rate in infants with tuberculosis, in tuberculous families, under 1 year of age, as reported by Calmette, would hold true for New York City. I therefore had to make statistics for control. There were 282 infants of families with tuberculosis who did not receive vaccine. These were followed by me from birth or from the early months of the first year. So far, the rate of mortality from tuberculosis is 8 per cent. This figure will undoubtedly change because only 66 per cent of the infants have finished their first year. In the vaccinated group, the mortality rate for tuberculosis is 1.6 per cent; however, only 40 per cent of them are over 1 year of age. The mortality from all causes among the infants vaccinated was 9.6 per cent, while the general mortality from all causes for the same period was 18.8 per cent.

All of the infants vaccinated and the infants used for control, are from families with tuberculosis. Not all of the infants have actually been exposed, because in some instances the persons with tuberculosis either had died before exposure was possible or had been removed from the home. Sixteen of the infants vaccinated are in close contact with open tuberculosis in their homes, and sixty-one are living in families in which one or more members have closed tuberculosis. In the cases used for control, the exposure is somewhat greater, because the group is made up from families who are not cooperative and who have come to me when the infants were more than 10 days of age.

All of the vaccinated infants who died were in hospitals, and necropsies were obtained in 50 per cent. Some of the control group did not die in hospitals, and only 33 per cent of them came to necropsy. The figures are more accurate for the vaccinated group than for the unvaccinated group. I am sure that not a single death from tuberculosis was missed in the group of infants inoculated with B. C. G.

Two vaccinated infants died of tuberculosis. Both deaths are difficult to explain. The mother of one died of miliary tuberculosis; the infant was not exposed. It is possible, however, that the infant had developed placental infection. The other was not separated from his father, who had tubercle bacilli in his sputum. Calmette urges one month of separation from the tuberculous parent after the vaccine is given. He says this time is necessary for the development of immunity. I am not always able to carry out this rule, because while the parents consent to the vaccination, they refuse to be separated from the infant.

I have observed interesting facts in the control group: 1. Thirty-seven per cent of the infants reacted positively to tuberculin within the first year. 2. The incidence of hypersensitiveness in children exposed to tuberculous mothers was no greater than in those exposed to tuberculous fathers. 3. In the children with negative Mantoux reactions, few showed parenchymatous involvement of the lung at roentgen examination. In the children with positive Mantoux reactions, changes in the lungs were rarely found. Those who died usually showed changes in the parenchyma.

The B. C. G. vaccine frequently gives a temporary hypersensitiveness. The steady positive Mantoux reactions are due to exposure to tuberculosis. Twenty-four per cent of the infants inoculated with B. C. G. had a positive reaction to the tuberculin test within the first year.

I never observed parenchymatous changes by roentgen examination among the infants inoculated with B. C. G., except in the two who died of miliary tuberculosis. The usual change is the enlarged shadow of the hilum, but this is indefinite among young infants. An x-ray picture showing changes in the lungs has bad prognostic significance.

Blood counts after vaccination were not reliable because of the great physiologic variations of the blood picture in new-born infants.

I found great numbers of B. C. G. bacilli in the stools from eight to thirty-one hours after vaccination.

This work is promising. The mortality from tuberculosis has decreased from 8 to 1.6 per cent. Whether this is due to the vaccine or to a coincidence I am unable to tell.

As Calmette does not believe that the hypersensitiveness and immunity parallel each other, the only control at present over the usefulness of the vaccine is carefully compiled mortality statistics.

DISCUSSION

DR. CHARLES HENDEE SMITH: When Dr. Park started this experiment two years ago, we were all skeptical and not convinced that the proof could be established by the methods which were planned. The experiment has shown a tremendous amount of work, and has brought out a good deal of valuable information. I think that we are not in a position at this time to be sure that feeding these children bacilli by mouth guarantees immunity. There are too many factors in Dr. Park's and Dr. Kereszturi's work which are conflicting. To me, in order to have a case of definitely proved immunity, there should be proof that the infant has been inoculated and then exposed to tuberculosis. If the infants escaped further infection, we would have a real answer to the problem. It is obvious that this is almost impossible to accomplish under the circumstances with which such an experiment must be conducted. Unless a child shows a positive tuberculin reaction the experiment shows nothing, because he has not been infected with the attenuated bacillus. I believe that children with negative reactions who have done well even in contact with tuberculous persons have just made lucky escapes.

Dr. Kereszturi mentioned sixty-one infants in families with closed tuberculosis, of which 45 per cent developed positive tuberculin reactions. The chances are that they developed it from bacilli which were in the sputum that was not examined. We all know that the "casual shedder" is one of the greatest dangers.

Dr. Park stated that good surroundings are a factor in this work. These children have undoubtedly had a better chance than others not under observation, for Dr. Kereszturi and her associates have gone into these families and have educated them concerning the proper care of the children. If this work has been of no other use, it has undoubtedly saved a good many lives by the mere fact that it has been done — but after all that is not what we are after. We know that good follow-up work and good care prevents or minimizes infection.

The Mantoux reactions which were positive and then became negative interest me very much. I have always believed that if the Mantoux test is positive it does not become negative, certainly not in a short time. There is always the possibility of false readings, for the equation for human beings always enters into the reading of chemistry tests.

It seems to me that these x-ray pictures are convincing only when they show massive pneumonia, definite disseminated tubercles or advanced miliary tuberculosis. I have believed for a long time that the size of the hilum shadows means nothing because of the normal variation. I have noticed that the good pictures of children under 1 year of age show nubbins or small shadows which in children more than 1 year of age, one would call calcified tubercles. One must be extremely conservative in interpreting x-ray pictures of these small infants.

I hope this paper will do what Dr. Park and Dr. Kereszturi desire, arouse more interest, supply more material and result in more hospitals that will take in these children, so that a larger amount of material can be collected.

Dr. Kereszturi's first statement that this is a preliminary paper for the purpose of arousing interest and of collecting more material is a good point of view. Most physicians with this much material to present to the Academy would present it as a finished subject.

DR. HOWLAND G. FREEMAN: The work that Dr. Park has organized should be most valuable as a critical study of a small group of cases.

In Paris last summer, Dr. Weill-Halle, who has been making injections into infants for Dr. Calmette, read a paper at the Hospital des Enfants Malades at a conference of pediatricians. Dr. Weill-Halle was convinced of the value of the work, but there was an active discussion, many questioning the efficiency of the results. In France, an enormous number of infants have been injected, but the impression is that they have not been efficiently followed up.

DR. BELA SCHICK: What I have to say is not in the way of discussion because I have had no personal experience in this work, but I also was in Paris last summer and met Calmette and saw something of his work. Not only that, but while visiting other countries, especially Austria and Germany, I heard other authors' opinions of this work. It is easily understood that Calmette and his staff are enthusiastic and that they have a large following. Their statistics comprise results for about 100,000 vaccinated children. The farther one goes from Paris, the more often one hears voices of doubt and opposition. This is especially so in Vienna, under the influence of Nobel's investigation, whereby he found that the B. C. G. bacillus when subcutaneously injected into guinea-pigs produced tuberculous manifestations which could be transmitted to other guinea-pigs. But even those in opposition admit that the administration of the Calmette vaccine by mouth is harmless. The only question, already mentioned by Dr. Smith, is whether the tubercle bacilli enter the organism and produce infection. In the majority of such cases the patients do not develop a positive tuberculin reaction, and I agree with Dr. Smith that this fact is rather against the assumption that the tubercle bacilli had gone through the intestinal wall. Calmette, of course, denies that a positive reaction must be expected after the administration of the vaccine by mouth, even if the tubercle bacilli pass the intestinal wall. Calmette believes that the negative tuberculin reaction does not exclude the development of immunity; however, that may be a theoretical difficulty. I think the only method of proving whether Calmette is correct or not is that which Dr. Park and Dr. Keresturi are employing; that is, using the Calmette method with all possible controls. As the whole question is of the utmost importance, it is our duty to assist Dr. Park and Dr. Kereszturi in their work.

DR. PARK: I hope that you will be influenced by what Dr. Smith said to help us, for it is only by such cooperation as Dr. Smith has given that we can hope to get sufficient material to form an opinion on the value of the vaccine.

Dr. Smith questioned that a positive tuberculin reaction later changed to a negative one. The tests on the calves were made by a trained veterinarian under the supervision of Dr. King of the Mount McGregor Sanatorium. There is no doubt in my mind that a clear cut reaction became weaker, then absent and finally, after being reinfected again, positive. At necropsy a well developed tuberculosis was shown. We are dealing with a live bacillus which is practically nonvirulent, and the lesions formed are usually temporary. Ordinarily, we are dealing with a virulent bacillus which produces persistent and usually progressive lesions. This difference may explain the temporary nature of the positive tuberculin reaction. Dr. Kereszturi will show that infants, like calves, may develop a temporary reaction.

DR. KERESZTURI: Almost all of the infants vaccinated with B. C. G. are given the Mantoux test frequently. Few of them persistently give a positive tuberculin reaction, but those who do are, in the majority of cases, exposed to some form of tuberculosis. Those infants who are not exposed either react negatively or give one or two positive reactions to Mantoux tests, and then lose their hypersensitiveness for tuberculin. In this type, the tuberculin test is rather less circum-

scribed and less infiltrated than in those who react permanently positive to tuberculosis. There is little chance that we made a mistake in reading these slightly positive, changing Mantoux reactions, because in the doubtful cases more than one person examined the results. In conclusion, we might say that the changing Mantoux reaction is due to the vaccine itself, and the persistent one to infection with human bacilli.

Just a few days ago, we received a similar report from Dr. Leon Bernard in Paris. He examined the hypersensitiveness of 120 infants vaccinated with B. C. G. at frequent periods, without exposing them to tuberculosis. He was able to observe the same type of changing Mantoux reactions as we did among our infants vaccinated with B. C. G., who were not exposed.

The majority of physicians in this country and in other countries are of the same opinion as Dr. Smith, i. e., they cannot imagine immunity for tuberculosis without a positive tuberculin reaction. Calmette himself is convinced that hypersensitivity and immunity do not parallel each other.

Concerning the other objection of Dr. Charles Hendee Smith — that the vaccinated group is more intelligent and cooperative than the control group, and that we are liable to pay more attention to them than we do to the control group — I wish to mention the following: We are careful to treat the two groups alike. Our aim is to improve the hygienic condition of all our patients as much as possible. It is true that some of the parents give consent to the vaccination because they are intelligent and want to do everything for the benefit of their children. On the other hand, we have a group of infants in which B. C. G. was used, the parents of whom signed the consent because they were indolent; they did not care what happened to their children. Probably, we have also somewhat more cooperative families among the vaccinated group, but the difference is not great.

In regard to the criticism of the x-ray pictures, I agree with Dr. Smith. It is hard to interpret them at such an early age. The position of the child and the stage of expiration or of inspiration, which one cannot control in so many cases, are all disturbing factors. If there is an antagonism between the results of the Mantoux test and the x-ray picture, we usually pay more attention to the tuberculin test.

Concerning the future of the problem, my belief is that the subcutaneous method will be the final solution. Before we change to this method, however, we want to be sure not only that it is better, but also that it is harmless. All the evidence suggests that the oral method is a less effective immunizing method than the subcutaneous one.

A Study of the Blood in Infants and Young Children. Martha Wollstein.

This paper will be published in full.

Book Reviews

Über die Aufzucht Fruhgeborener Kinder im Basler (Switzerland) Kinderspital und Deren Ergebnisse von 1922 bis 1927. By A. Hottinger. Paper. Price, 8.40 marks. Pp. 136, with 51 illustrations. Berlin: S. Karger, 1928.

This excellent monograph is divided into two parts. In Part 1, the author writes first of the care of premature infants; second, of the mortality and detailed treatment, with the special causes of death, and third, morbidity, with details covering dyspepsia, icterus, birth trauma, syphilis, spasmophilia, anemia, grip and secondary intestinal conditions. In part 2 he deals specifically with rickets, as seen in the premature infant. He first writes of the analogy and the differences in the course of rickets between the full term and the premature infant. The next chapters cover the relationship between the frequency of rickets and the following observations: the birth weight and season; the early diagnosis as related to clinical and roentgenologic data; the later diagnosis made from roentgenologic data; serum and urinalyses; histologic examination — this chapter is well illustrated by photomicrographs, and covers a study of thirty-three premature and twenty-seven full term infants used as controls — and, in the final chapter, the therapy and prophylaxis of rickets — this chapter covering experiences with calcium lactate, metallic phosphorus, cod liver oil, yolk of egg, radiation, irradiated milk, and irradiated ergosterin. The bibliography is complete.

Clinical Gynecology and Obstetrics. By R. T. La Vake. Price, $4. Pp. 281, with illustrations. St. Louis: C. V. Mosby Company, 1928.

The primary purpose of the author has been to provide a book for students and general practitioners, which will present the problems of gynecology and obstetrics without the confusing volume of material found in special textbooks. This has been accomplished by terseness of style and practical selection of the material which is presented as in a clinic.

The book is divided into two parts. Part 1 deals with the problems of diagnosis and treatment in gynecology and obstetrics. Special emphasis has been placed on the gynecologic examination and diagnosis of pregnancy, prenatal care, discharges and infection. Foci of infection as the positive factor in complications of pregnancy is an observation worthy of note.

Part 2 deals with the specific problems of pregnancy and labor. The chapter entitled "Alleviation of Pain During Labor" and "Rules of Obstetrics," are deserving of special attention.

The book has decided value as a practical and easily available reference.

Tuberculose Infantile. By H. Barbier. Price, 25 francs. Pp. 254, with 85 illustrations. Paris: J. B. Baillière et fils, 1928.

This book is one of the set entitled, A New Treatise of Medicine and Therapeutics, edited by Carnot and Lereboullet. It is devoted exclusively to the study of the anatomic and clinical forms of pulmonary tuberculosis in infants from the first month to the eleventh year of life. The first two thirds of the book is devoted to the various forms of the lesions with a microscopic study of the anatomy involved. This is done thoroughly. The remainder of the book presents the different aspects of the infection through the different age periods. Prophylaxis and vaccination occupy a scant three pages, and treatment five pages. The work of Calmette is dismissed with a short paragraph. While the pathology is thoroughly discussed, nothing particularly new is added to the general knowledge of the disease.

THE PRINCIPLE OF INFANT NUTRITION AND THEIR PRACTICAL APPLICATION. K. H. TALLERMAN and C. K. J. HAMILTON. Price, 10 shillings. Pp. 183. London: William Heinemann, 1928.

The subject matter is set forth with singular clarity and simplicity; yet the presentation is not in any sense dogmatic. Details are sufficient to give the student an understanding of the principles involved in infant feeding without confusing him. The headings of the chapters are: I. Physiology and Bacteriology, II. Nutritional Requirements During Infancy, III. Breast Feeding, IV. Nutritional Disturbances in the Breast-Fed Infant, V. The Premature Infant, VI Artificial Feeding of Normal Infants, VII. Nutritional Disorders of Infancy, and VIII. Weaning and the Diet from Nine Months Until Two Years of Age.

FOOD, NUTRITION AND HEALTH. By E. V. MCCOLLUM and NINA SIMMONDS. Price, $1.60. Pp. 148. Baltimore: published by the authors, 1928.

This is the second edition of this book which was written to meet the need of the general public for a nontechnical account of the results of modern researches on foods and nutrition. It presents the essential facts of what diet can and cannot accomplish. The book is concise and extremely readable, as the great mass of experimental data which usually cumbers a book of this type has been omitted. It makes an excellent textbook for the lay person, whose ideas may have been badly jumbled by faulty reading of the voluminous literature on the subject of nutrition.

Directory of Pediatric Societies

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SECTION ON DISEASES OF CHILDREN

Chairman: Dr. W. A. Mulherin, 753 Broad St., Augusta, Ga.
Secretary: Dr. C. A. Aldrich, 545 Lincoln Ave., Winnetka, Ill.
Place: Portland, Ore. Time: July 8-12, 1929.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Henry L. K. Shaw, 142 Washington Ave., Albany, N. Y.
Secretary: Dr. Howard Childs Carpenter, 1805 Spruce St., Philadelphia.
Place: St. Louis. Time: 1929.

THE ASSOCIATION OF AMERICAN TEACHERS OF THE DISEASES OF CHILDREN

President: Dr. Paul W. Emerson, 86 Bay State Road, Boston.
Secretary: Dr. Ralph M. Tyson, 1527 Pine St., Philadelphia.
Place: Portland, Ore. Time: July 8-12, 1929.

AMERICAN CHILD HEALTH ASSOCIATION

President: Hon. Herbert Hoover, 370 Seventh Ave., New York.
Secretary: Dr. Philip Van Ingen, 370 Seventh Ave., New York.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. Thomas Crossan Clark, 51 Herkimer St., Hamilton, Ont.
Secretary-Treasurer: Dr. Frank H. Boone, 164 James St. S., Hamilton, Ont.

SECTIONAL

CENTRAL STATES PEDIATRIC SOCIETY

President: Dr. J. Gurney Taylor, 120 E. Wisconsin St., Milwaukee.
Secretary: Dr. A. H. Parmelee, 310 S. Michigan Ave., Chicago.
Place: Milwaukee. Time: October, 1929.

SECTION ON PEDIATRICS OF SOUTHERN MEDICAL ASSOCIATION

Chairman: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. A. J. Waring, De Renne Apts., Savannah, Ga.
Place: Miami, Fla. Time: Nov. 20-22, 1929.

LOCAL

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. W. L. Channell, Medical Bldg., Oakland, Calif.
Secretary: Dr. J. E. Parrott, Medico-Dental Bldg., San Francisco.
Place: Various Teaching Schools. Time: Monthly.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. George P. Laton, 1136 W. 6th St., Los Angeles.
Secretary: Dr. William Sidney Bowers, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

THE ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. W. Wiley Jones, Majestic Bldg., Denver.
Secretary: Dr. Berryman Green, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: Third Saturday of each month, 2:30 p. m., September to May, inclusive.

GEORGIA PEDIATRIC SOCIETY

President: Dr. W. N. Adkins, Medical Arts Bldg., Atlanta.
Secretary and Treasurer: Dr. E. N. Gleaton, 212 E. Gaston St., Savannah.

PEDIATRIC SECTION OF FULTON COUNTY MEDICAL SOCIETY, ATLANTA, GA.

Chairman: Dr. Willis Ragan, Medical Arts Bldg., Atlanta.
Secretary: Dr. Lee Bivings, Exchange Bldg., Atlanta.
Place: Academy of Medicine, 32 Howard St., Atlanta. Time: Second Thursday of each month from October to April, at 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

Chairman: Dr. William W. Howell, 279 Clarendon St., Boston.
Secretary: Dr. Randolph K. Byers, 66 Commonwealth Ave., Boston.
Place: Boston Medical Library. Time: Second Friday of each month.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Maurice Blatt, 185 N. Wabash Ave., Chicago.
Secretary: Dr. J. K. Calvin, 104 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. L. R. De Buys, 1417 Delachaise St., New Orleans.
Secretary-Treasurer: Dr. C. T. Williams, 7401 Burthe St., New Orleans.

DETROIT PEDIATRIC SOCIETY

President: Dr. M. Boyd Kay, 10 Peterboro St., Detroit.
Secretary: Dr. Charles A. Wilson, 71 E. Ferry St., Detroit.
Place: Children's Hospital of Michigan. Time: No fixed date; approximately once a month.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Ray Shannon, Lowry Bldg., St. Paul.
Secretary: Dr. E. S. Platou, 730 La Salle Bldg., Minneapolis.
Place: University Campus and Rochester. Time: Winter, Spring, Summer, Fall.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Park J. White, Beaumont Bldg., St. Louis.
Secretary-Treasurer: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Place: St. Louis Children's Hospital. Time: At least once a year and contingent thereafter on the arrangement of a suitable program.

NEBRASKA-IOWA PEDIATRIC SOCIETY

President: Dr. Floyd Clarke, City Nat'l Bank Bldg., Omaha.
Secretary: Dr. R. B. Eldredge, Medical Arts Bldg., Omaha.
Place: Add-Sell Restaurant. Time: Second Thursday of each month from October to May, inclusive, 6 p. m.

BROOKLYN PEDIATRIC SOCIETY

President: Dr. Louis M. Ruderman, 961 Eastern Parkway, Brooklyn.
Secretary: Dr. Joseph F. Paulonis, 1357 Bushwick Ave., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

BRONX PEDIATRIC SOCIETY

President: Dr. William Hinz, 1964 Grand Concourse, New York.
Secretary: Dr. L. H. Barenberg, 1749 Grand Concourse, New York.
Place: Concourse Plaza, 161st St. and Grand Concourse, New York.
Time: Second Wednesday of each month, except June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various Cities in New York. Time: Fourth Thursday of October, January and April.

PEDIATRIC SECTION OF THE NEW YORK ACADEMY OF MEDICINE

President: Dr. Stafford McLean, 17 East 71st St., New York.
Secretary: Dr. F. Elmer Johnson, 300 West End Ave., New York.
Place: New York Academy of Medicine, 2 East 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester, N. Y.
Secretary: Dr. Edwin R. Reynolds, 1620 St. Paul St., Rochester, N. Y.
Place: Arranged by Program Committee. Time: First Friday of each month from October to May.

THE PEDIATRIC SECTION OF THE ACADEMY OF MEDICINE OF CLEVELAND

Chairman: Dr. C. W. Wyckoff, 8314 Euclid Ave., Cleveland.
Secretary: Dr. C. L. Ruggles, 10616 Euclid Ave., Cleveland.
Place: 2009 Adelbert Road. Time: Four meetings, from September to May.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Edward L. Bauer, Jefferson Medical College, Philadelphia.
Secretary: Dr. John Porter Scott, 2040 Pine St., Philadelphia.
Place: College of Physicians, 19 S. 22nd St., Philadelphia. Time: Second Tuesday of each month from October to June, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Zaccheus R. Scott, Westinghouse Bldg., Pittsburgh.
Secretary: Dr. Theodore C. Elterich, Highland Bldg., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. W. D. Blue, 1024 Madison Ave., Memphis, Tenn.
Secretary: Dr. Gilbert J. Levy, 899 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month.

TEXAS PEDIATRIC SOCIETY

President: Dr. Edwin G. Schwarz, Medical Arts Bldg., Fort Worth.
Secretary-Treasurer: Dr. Ramsey Moore, Medical Arts Bldg., Dallas.

RICHMOND PEDIATRIC SOCIETY

President: Dr. T. D. Jones, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. W. Ambrose McGee, West End Medical Bldg., 2618 Grove Ave., Richmond, Va.
Place: Westmoreland Club, 601 E. Grace St., Richmond, Va.
Time: First Thursday of each month (other than during the summer).

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Charles E. Conrad, Harrisonburg.
Secretary: Dr. William B. McIlwaine, Petersburg.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. E. D. Carder, 736 Granville St., Vancouver, B. C.
Secretary and Treasurer: Dr. George A. Lamont, 736 Granville St., Vancouver, B. C.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Arthur H. Gray, Lumber Exchange Bldg., Seattle.
Secretary: Dr. Armin Rembe, Stimson Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, at 7 p. m.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. A. L. Kastner, 120 E. Wisconsin St., Milwaukee.
Secretary: Dr. F. R. Janney, 418 E. North Ave., Milwaukee.
Place: Children's Hospital, Milwaukee. Time: Second Wednesday of each alternate month, beginning with February.

PEDIATRIC SECTION, ACADEMY OF MEDICINE, TORONTO

Chairman: Dr. F. R. Hassard, 1361 King St. West, Toronto.
Secretary: Dr. G. A. Davis, 12 Belsize Dr., Toronto.
Time: November 17, December 15, February 16 and March 15.